ARCHIVES OF OPHTHALMOLOGY

VOLUME 31 (old series Volume 88) JUNE 1944 NUMBER 6

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EVALUATION OF OCULAR ANGIOSPASM

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Pendulums, as is well known, have a way of swinging. When an idea has served to explain one condition satisfactorily, the attempt is invariably made to use it for other purposes, and the pendulum is set in motion. The concept of angiospasm is by no means new, but the attempt to explain a number of pathologic ocular conditions as due to that entity is largely an effort of recent years. My own interest in the subject began with a study of Krogh's [1] work on the capillaries, originally published in Müller's atlas [2] (1922), and some applications of this work to ocular conditions by Scheerer, Parrisius and Mayer-List,[3] in the University of Tübingen. Out of this work arose the concept of a vasoneurotic diathesis. When the peripheral circulation was studied by various methods, certain persons were found to have an abnormally labile vasomotor system. In response to various stimuli, especially cold, to certain drugs, such as nicotine, and, in some cases, to certain foreign proteins, these persons showed signs of spasm involving the peripheral vessels, with resulting stasis in the capillary circulation. The capillaries themselves, although devoid of a true muscular coat, are narrowed, as Krogh has shown, by contraction of the Rouget cells in their walls, and in persons with vasoneurotic diathesis such contractions are easily provoked and are abnormally pronounced and prolonged.

In the earlier work reliance was placed chiefly on capillary microscopy, and patients with various ocular conditions were studied by this method. It was thought at first that patients with glaucoma often showed signs of the vasoneurotic diathesis; but the evidence was by no means convincing, and Mielke [4] noted no such relationship in his series. Attempts were made by Scheerer and others to determine vasoneurotic signs by a study of entoptic phenomena, but these efforts were not particularly successful.

As the study of peripheral vascular diseases has progressed, a series of observations and tests have been developed which determine with a fair degree of accuracy which patients have a pathologic degree of peripheral angiospasm. Dr. Gilbert Marquardt has furnished me with information concerning these special methods of examination, and he, as well as Dr. Géza de Takats, Dr. Theodore Van Dellen and Dr. J. F. Mallach, supplied me with data on patients sent them for examination. Few ophthalmologists are qualified to make these examinations, and it is unfortunately true that many internists are not sufficiently interested in the subject to provide the desired information. The examination should include a careful history. Patients with vasoneurotic diathesis usually note undue distress on exposure of the extremities to cold. Their hands become white when elevated and flushed, or even cyanotic, when dependent. They take particular care to protect the extremities against cold so as to avoid various unpleasant symptoms.

Examination should really be carried out in an air-conditioned room, but it is usually sufficient if the room is free from drafts and the patient is allowed to rest in such a room for a half-hour before examination. This precaution is taken to avoid the rapid changes which occur in persons with vasoneurotic disturbances when exposed to changes in temperature. Observation of the extremities confirms the statements in the history. The hands and feet are pale, and readings with a skin thermometer show an abnormal difference between the oral temperature and the temperature of the extremities. A difference of 3 or 4 degrees (F.) is normal, while vasoneurotic persons show differences as high as 10 degrees. The use of nicotine, as in smoking a cigaret, will cause a further drop in the peripheral temperature of susceptible persons of 6 to 12 degrees (F.). Normal persons may show a drop of 4 to

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Read at the Forty-Eighth Annual Session of the American Academy of Ophthalmology and Otolaryngology, Oct. 10-13, 1943, Chicago.

1. Krogh, A.: The Anatomy and Physiology of Capillaries, New Haven, Yale University Press, 1922.

2. Müller, O.: Die Kapillaren der menschlichen Körperoberfläche in gesunden und kranken Tagen, Stuttgart, Ferdinand Enke, 1922.

3. Scheerer, R.: Zentralbl. f. d. ges. Ophth. **29**:257, 1933. Scheerer, R.; Parrisius, W., and Mayer-List, R.: Klin. Monatsbl. f. Augenh. **73**:29, 1924.

4. Mielke, S.: Arch. f. Augenh. **110**:236, 1936.

5 degrees (F.) under these conditions. In 1 of our patients this drop amounted to 13 degrees (F.). Oscillometric readings are low. The pulse in one or both posterior tibial arteries may be weak or imperceptible. Microscopic study of the capillaries of the nail folds shows narrowing of the arterial limb of the capillary loops, with stasis, small aneurysms and hemorrhages in a number of areas.

When these tests have been completed and the temperature of the extremity has returned to the original level, blocking of the posterior tibial nerve is employed in patients with signs of spasm. In patients without organic changes in the vessels, a group which includes most of the younger patients with this disturbance, the temperature rises after nerve block so as to approximate the oral temperature. In patients with arteriosclerotic or thrombophlebitic changes the rise in temperature is less, or may be absent.

The blood pressure of the younger patients in the vasoneurotic group is low or normal. After the cold pressor test (dipping the hand in ice water) little, or no, rise in blood pressure occurs. When a rise of pressure does occur, the condition is considered to be early or latent hypertension, and hence in a different category from the vasoneurotic disturbance in which my colleagues and I have been most interested. The factor of peripheral spasm in patients with hypertension is of great importance, but I wish to emphasize the fact that a number of young persons show severe peripheral angiospasm without elevation of the systemic blood pressure. The relation of this condition to Buerger's disease (thromboangiitis obliterans) and Raynaud's disease will be discussed later.

A few other tests may produce information of value. The ascorbic acid of the blood is often low, even in persons receiving a normal diet. The basal metabolic rate is low and the cholesterol of the blood high in a few instances, and the amount of noniodizable calcium in the blood may be low. There may be relative achlorhydria, according to Marquardt, although gastric analysis was not done in most of our cases.

Undoubtedly, there are a number of persons with vasoneurotic disturbances who show no pathologic condition of the eyes, and in certain patients with ocular lesions of various types a tendency to peripheral angiospasm may be revealed which has no relation to the ocular condition. My reference to the swinging of the pendulum was prompted chiefly by the work of Duggan.[5] He has emphasized the factor of angiospasm in a variety of conditions, many of which were considered, for what seemed good and sufficient reasons, to be of inflammatory origin. While local vascular spasm may play a part in the edema which accompanies inflammation, Duggan's work seems to have resulted in a certain confusion. Attention has been directed away from a search for the causative factor in these conditions, and the supposed effect of treatment by vasodilators has, it seems to me, been unduly emphasized. In most of his cases the pressor tests previously described were not done, and treatment was empiric.

5. Duggan, W.: Am. J. Ophth. **26**:354, 1943.

CENTRAL ANGIOSPASTIC RETINOPATHY

It is the purpose of this communication to describe a few fairly well defined types of pathologic processes involving the eyes, chiefly two, in which peripheral angiospasm seems to be the causative factor, and to urge that patients presenting signs suggestive of these conditions be submitted to an examination which will determine whether or not abnormal peripheral angiospasm is present.

The most important of these conditions is what Marquardt and I[6] called central angiospastic retinopathy. In the use of this term we followed Horniker, but we preferred the term retinopathy to that of retinitis. The term retinitis seemed to us especially unfortunate, since it is our conviction that the condition is not inflammatory, but is due entirely to a circulatory disturbance.

In our former communication[6] the literature was reviewed, and reasons even were given for identification of this condition with that described by a number of previous authors under various names. These terms included central recurrent retinitis (von Graefe), retinitis centralis (Asayama), retinitis centralis annularis (Kraupa), choroiditis centralis serosa (Riehm), preretinal edema (Guist) and idiopathic flat detachment of the retina (Walsh and Sloan). In most of the reports by these authors, the condition was claimed to be inflammatory, and, as usual, tuberculosis was invoked as the probable cause. This was done by the reporters of a remarkable series of cases in Japan. Matsuoka, for example, collected the records of 640 cases, and Kitahara reported 150 cases in his personal experience. In view of what is now known of the condition, one may add to various more or less scientifically verified impressions of the Japanese the conviction that they certainly must be a spastic little people. A few authors, such as Kraupa and Fuchs, suspected the circulatory origin of the condition, but it remained for Horniker, in 1927

6. Gifford, S. R., and Marquardt, G.: Central Angiospastic Retinopathy, Arch. Ophth. **21**:211 (Feb.) 1939.

to 1937,[7] to look for other signs of angiospasm and to find them in most of his 42 cases. His methods of examination were not as accurate as those employed at present, but the response of his patients to the use of sedatives and vasodilators must be considered additional evidence that the condition he described was due to spasm of the smaller retinal vessels or, in some cases, of the capillaries themselves.

Early Series.—Our report[6] dealt with 8 patients. In 6 the condition was typical in that only the area of the macula was involved, while in 2 patients some of the larger retinal vessels were also occluded. Special examination of the peripheral vascular system was made in only 6 patients, all of whom showed evidence of angiospasm (table). All 8 patients were males, between 17 and 43 years of age. Nearly all smoked. The typical picture was that of sudden reduction of central vision. This varied from a slight loss, with a small relative central or paracentral scotoma, to a reduction to 20/200. Either one or both eyes were involved, and often there was a history of previous attacks. Metamorphopsia was a common symptom in cases in which there was slight visual loss. During the acute attack the predominant change in the fundus was edema, involving either the whole macular area or some part of it (figure, *A*). With the fine beam of the Friedenwald ophthalmoscope, this area was seen to be distinctly elevated, as shown by bending of the beam. The splitting of the beam described by Walsh and Sloan, which led them to diagnose the condition in their cases as flat detachment of the retina, was not seen, and for a number of reasons it was considered that swelling was present in the retina itself, particularly in the nerve fiber layer. The transient hyperopia observed in several patients suggests an actual elevation of the retina in these persons. A striking feature presented by several patients was a pronounced circular reflex surrounding the macular area, and localization of this reflex with the fine beam seemed to confirm Guist's opinion that it represented an elevation of the internal limiting membrane due to edema fluid. Small hemorrhages were seen at the ends of the visible vessels in only a few patients. The larger retinal vessels were normal in most cases, although constriction of one or more vessels was evident in a few instances and obliteration of several branch arterioles had occurred in 1 case. The occurrence of the edema without involvement of the visible vessels was what led to the conclusion that the capillaries themselves were affected, an opinion shared by Horniker and Bailliart.[8]

Results of Special Examinations in the Reported Cases

Case No.	Average Blood Pressure, Mm.	Oscillometric Data on Ankle: Before Treatment	Oscillometric Data on Ankle: After Treatment	Temperature of Toes: Before Nerve Block	Temperature of Toes: After Nerve Block	Degree of Capillary Spasm *	Acrocyanosis of Toes	Reaction After One Cigaret	Treatment
2	118/80	3.0+	3.0+	32 C. (89.6 F.)	34 C. (93.5 F.)	++++	..	Drop of 4.6 degrees C. (8.2 degrees F.)	Stopped smoking; phenobarbital
4	124/80	2.0	3.0+	28.6 C. (83.4 F.)	32.4 C. (90.3 F.)	++	++	Drop of 4 degrees C. (7.2 degrees F.) in 6 min.	Tissue extract; phenobarbital; thyroid; stopped use of tobacco
5	130/80	1.5	.....	27.4 C. (81.3 F.)	33.2 C. (91.7 F.)	++++	++	Drop of 5 degrees C. (9 degrees F.)	Stopped smoking; phenobarbital
6	120/70	2.0	2.0	33 C. (91.4 F.)	35.2 C. (95.3 F.)	++	+	Drop of 3.2 degrees C. (6.7 degrees F.)	Stopped smoking; phenobarbital; typhoid vaccine intravenously; tissue extract
7	144/90-104/68; low reading after nitrite therapy	1.5	3.0+	25 C. (77 F.)	31.2 C. (88.1 F.)	++++	++	Formerly smoked; drop not measured	Nitrites; tissue extract; typhoid vaccine given intravenously; treated 6 days; stopped smoking
8	128/82	1.0+	3.0+	29.2 C. (84.5 F.)	32.8 C. (91 F.)	++++	++++	Drop of 4.6 degrees C. in 5 min.	Tissue extract; phenobarbital for 6 mo.; stopped smoking

* Observations by capillary microscopy.

In all but 1 of these first 8 patients, restoration of normal vision occurred within two to six weeks, in response to what we called antispasmodic therapy. The edema was replaced in these patients by absorption of fine retinal pigment, which sometimes involved an area larger than the macula (figure, *B*). In some patients fine granular pigment appeared in the macular area; in 1 patient the choroidal vessels became visible, with a line of pigment about the defective area. In a few patients, on whom subsequent reports were furnished by other ophthalmologists, the fundi were said to have returned to normal, but in all patients followed personally signs of absorption of the retinal pigment were observed. In a number of patients, the fine white

7. Horniker, E.: Ann. di ottal. e clin. ocul. **55**:578 and 686, 1927; Arch. f. Ophth. **123**:286, 1929; Klin. Monatsbl. f. Augenh. **98**:487, 1937.

8. Bailliart, P.: Ann. d'ocul. **171**:97, 1934; **175**: 133, 1938.

spots, seen by Horniker and Bailliart and erroneously described by them as Gunn dots, were noted.

In none of these 8 patients have recurrences been reported. Most of the patients continued to refrain from smoking, and some continued under moderately intensive antispasmodic therapy for a considerable period. With this therapy most patients gained weight and reported improvement in general health.

Present Series.—Clinical Data: Since the study of this early series, I have seen 23 additional patients with a disturbance which it was felt belonged to this category. Fifteen of these patients were sent to Dr. Marquardt, Dr. Van Dellen, Dr. Mallach or Dr. de Takats for pressor tests. Sixteen were seen during an acute attack, with the typical picture just described. Five were seen only after the edema had subsided; they presented the slight degenerative changes described in this postspastic period. Of these 23 patients, all who were followed showed recovery of normal, or nearly normal, vision. In a few patients vision remained reduced to 20/30 or 20/25, with persistence of a small relative central scotoma. Several patients were seen only once in consultation and were not followed. In 2 patients the changes were more severe and of such character as to cast doubt on the diagnosis or to modify the picture of the condition previously formed. One of these patients, a woman aged 31, presented a typical fundus picture when she was first seen, with the visible vessels normal and extreme macular edema with radiating white deposits, the appearance resembling a macular star. The blood pressure was normal. Vision was reduced to 5/200 and after three months had returned only to 20/100. Some macular edema was still present.

The second patient, a woman aged 30, was observed by Dr. Roy Riser for more than a year. The sharply circumscribed macular edema with a circular reflex was typical, but pictures of the fundus taken during this time showed practically no change in the condition. Vision could be improved by a + 3.00 D. sphere to 20/25, though a relative scotoma was present. The other eye was normal. Pressor tests were not made.

The ages of these 23 patients, with 1 exception, ranged from 25 to 45, with an average of 36 years. The exception was a man aged 21, with normal blood pressure, pronounced pressor reactions, especially to tobacco, and recovery under antispasmodic treatment, with abstinence from tobacco. Whereas in the earlier series only men were affected, of these 23 patients, 8 were women. A number of these women smoked, a few to excess. Their ages ranged from 28 to 40. One showed, in addition to the signs of peripheral angiospasm, evidence of pseudo Addison's disease, with abnormally low systemic blood pressure and a basal metabolic rate of — 20 per cent. In addition to these 23 patients, there were at least 4 in whom spasm of the fine vessels supplying the macula appeared in association with generalized arterial hypertension. Other signs of peripheral angiospasm were present in 2 of these patients, the only ones submitted to the tests, and antispasmodic therapy seemed to be of benefit for the ocular, as well as the systemic, condition, although restoration of function was never so complete as in the younger patients without systemic hypertension.

Owing to the absence of Dr. Marquardt and Dr. Van Dellen on military duty, and the fact that the examinations were conducted in several offices and hospitals, it is impossible to prepare

A, acute stage in a case of central angiospastic retinopathy; *B*, healed stage.

a table of vascular data including all the points covered in the first report, and in some cases the data seem incomplete. Of the 15 patients referred for special examination, however, all but 2 showed some evidence of abnormal peripheral angiospasm. One of these, a man, had a small healed lesion resembling the lesions developing later in this condition. He showed no signs of retinal edema during observation. The other, a man of 42, gave negative reactions in the pressor tests but had a history of great discomfort on exposure to cold and presented a basal metabolic rate of — 22 per cent. He did not smoke. His condition cleared completely on administration of thyroid and injections of tissue extract. Recheck during antispasmodic therapy in a number of cases showed improvement in the degree of angiospasm, the results in some instances approaching normal. It is recognized, however, that the tendency to peripheral angiospasm in most patients a hereditary constitutional anomaly and that measures to prevent or minimize spasm, especially protection against cold and abstinence from tobacco, will always be indicated for these susceptible persons.

Treatment: The treatment employed for most of these patients, in whole or in part, was as follows:

1. Complete abstinence from tobacco was advised, and the body was protected against cold.

2. In the acute stage intravenous injections of papaverine hydrochloride, ½ grain (0.032 Gm.) twice daily, were given for several days, followed by oral administration of ½ grain of the drug three times a day for one to two weeks.

3. In some cases intravenous injections of typhoid vaccine were employed for the vasodilating effect. Small doses, of 10,000,000 to 20,000,000 organisms, seemed as effective for this purpose as larger doses.

4. Use of a hypnotic, either combined with a diuretic in the form of a preparation of theobromine and phenobarbital sodium (theominal), 1 tablet (5 grains [0.325 Gm.] of theobromine and ½ grain of phenobarbital sodium) three times a day, or as phenobarbital, ½ grain three times a day, was continued for several months.

5. Tissue extract, usually an insulin-free pancreatic extract (depropanex), was injected intramuscularly, in a dose of 1 cc. twice a week for fourteen injections, the course being repeated in several cases.

6. The nitrites, including injection of a 10 per cent solution of sodium nitrite by vein, as advised by Duggan, were employed in some cases, but according to Marquardt, the effect of these substances on the small vessels or capillaries is neither as marked nor as prolonged as that of papaverine and the barbiturates, especially a combination of the two.

7. The parasympathomimetic drug neostigmine bromide, in doses of 7.5 to 15 mg. by mouth three times a day, had apparently a good effect.

8. Nicotinic acid was given, either as vitamin B complex or in pure form, in a dose of 150 mg. a day. Its effect on the capillaries was especially notable.

9. A diet containing calcium and the essential vitamins was advised, supplemented when indicated by concentrates of vitamin C and vitamin B complex.

10. Five patients whose basal metabolic rate was lowered received thyroid, and a few women with menstrual disturbance were given an estrogen.

11. A regimen including plenty of rest and avoidance of fatigue and nervous strain was advised when it seemed practical.

12. Checks were made by means of the pressor tests on a number of patients as an indication of the need for further treatment. Patients were advised against resumption of smoking at any time, and use of small doses of barbiturates was continued for some time or was resumed when signs of nervous tension or insomnia developed.

Comment.—Only a few reports on this condition have come to my attention since our early report. Duggan [9] seems to have observed 6 cases of the typical condition previously described, acute attacks responding to the use of vasodilators. He included as instances of a chronic form of the disease 3 cases which seem to me doubtful and 4 cases which he admitted fell in the category of disciform degeneration of the macula. This seems to confuse the issue, and few ophthalmologists would agree with Duggan's statement that "disciform degeneration differs only in degree from the mild lesions of choroidosis seen in young adults." His preference for the name "choroidosis centralis serosa" rests on certain debatable points, which need not be discussed here. No pressor tests were recorded in his brief case report, a positive response to the nitrites evidently being considered sufficient to confirm the diagnosis of angiospasm. Schaub [10] reported 1 case in which the fundic picture seemed typical but recovery

9. Duggan, W. F.: Choroidosis Centralis Serosa: Diagnosis, Pathologic Physiology and Therapy, Arch. Ophth. **27**:123 (Jan.) 1942.

10. Schaub, C. F.: Am. J. Ophth. **24**:1312, 1941.

was extremely slow. Löwenstein [11] reported 3 cases and suggested that allergy was a probable factor in certain cases. Smitmans [12] observed 9 cases in one year of a condition which he diagnosed as central serous choroiditis. In all cases normal vision was recovered after treatment with calcium, vitamins and papaverine. The earlier literature was reviewed in our previous report.[6]

PERIPHLEBITIS OF THE RETINA

Next to central angiospastic retinopathy, the ocular condition in which the question of retinal angiospasm seems to be of most interest is periphlebitis retinae with recurring hemorrhages in the vitreous. Marchesani,[13] in 1934, first suggested that patients with periphlebitis, a condition usually considered due to tuberculosis, might have a disease of the retinal vessels comparable to Buerger's disease of the extremities, and this theory seemed to be confirmed by examination of the peripheral circulation in his cases. He reported 25 cases, in 3 of which gangrene of the extremities required amputation, while in most of the cases only signs of "latent" thromboangiitis of the extremities were present, as revealed by examination of the extremities and capillary microscopy. In 7 of his cases, in which examination was made by Stander, there was evidence of involvement of the cerebral vessels, including oculomotor paralysis. In 1 of his cases sections of one eye showed thromboangiitis obliterans of the retinal and uveal vessels and no evidence of tuberculosis. Closure of retinal vessels has been described by Lisch [14] and Uyama [15] in cases of Buerger's disease. Lisch,[16] however, in a later study of 35 cases of various forms of peripheral vascular disease, including Buerger's and Raynaud's disease, did not observe periphlebitis. Schmidt [17] observed no signs of peripheral angiospasm in 8 cases of periphlebitis, in all of which there was evidence of tuberculosis.

In view of this somewhat uncertain status of the subject, it seemed of interest to report the observations on a series of patients with such a condition who had been seen since 1939. Of 12 such patients, 7 were referred for examination of the peripheral vascular system. No patient with hypertension, nephritis or diabetes was included, or any in whom trauma was a factor. Patients showing evidence of past or present iritis or choroiditis were also excluded.

The patients were selected on the basis of evidence of severe vascular disease of the retina of the type usually called periphlebitis, with, in nearly all, spontaneous hemorrhages into the vitreous and a tendency to the formation of preretinal bands of connective tissue. Most of the patients were young adults, the average age being 28.6 years at the onset of ocular symptoms. The oldest patient was 42 and the youngest 8 years of age. Eight patients were males and 4 females. In 7 patients more or less satisfactory evidence of tuberculosis was found, consisting chiefly of positive reactions to high dilutions of tuberculin given intradermally and, in some, positive signs in the chest. Their cases will not be discussed further, except for those of 2 who showed evidence of peripheral vascular disease as well. One patient presented no evidence of tuberculosis and was seen before pressor tests were advised. Several foci of infection were removed, and he has been free of recurrences for seven years. Five of the 7 patients referred for examination of the peripheral vascular system showed evidence of peripheral angiospasm, and in 3 of these it was the only factor which could be considered of etiologic importance. Two showed no evidence of angiospasm. One was tuberculin positive, while no etiologic factor could be discovered for the other.

The cases of the 2 patients showing evidence both of tuberculosis and of peripheral angiospasm may be discussed briefly.

A woman aged 25 gave a positive reaction to tuberculin; her basal metabolic rate was —26 per cent, and the cholesterol content of the blood, 187 mg. per hundred cubic centimeters; the pressor tests gave positive results, including a drop of 7.2 degrees (F.) in the temperature of the extremities after smoking. Her condition cleared up on treatment with thyroid and injections of foreign protein, without any tuberculin, and she has remained free of recurrences since she moved to a warmer climate. The changes were early in her case, permitting restoration of 20/15 vision in the only eye affected. It seems at least possible that the vascular condition was of importance in this case.

A man of 43 presented typical periphlebitis retinae, with perivascular sheathing, closure of a number of retinal veins and preretinal hemorrhages, which had organized and showed an ingrowth of new vessels. The reactions to tuberculin were positive, but after a long course of tuberculin therapy, when the reaction was negative, fresh areas of periphlebitis continued to develop. He was referred to Dr. de Takats, who found evidence in the extremities of Buerger's disease. There were absence of pulsation in one dorsalis pedis artery

11. Löwenstein, A.: Brit. J. Ophth. **25**:369, 1941.
12. Smitmans: Klin. Monatsbl. f. Augenh. **105**:733, 1940.
13. Marchesani, O.: Klin. Monatsbl. f. Augenh. **93**: 214, 1934. Marchesani, O., and Stauder, K. H.: Arch. f. Augenh. **109**:281, 1935. Marchesani, O.: ibid. **109**: 124, 1935.
14. Lisch, K.: Klin. Monatsbl. f. Augenh. **99**:812, 1937.
15. Uyama, Y.: Arch. f. Ophth. **137**:438, 1937.
16. Lisch, K.: Klin. Monatsbl. f. Augenh. **102**:228, 1939.
17. Schmidt, R.: Arch. f. Ophth. **142**:1, 1940.

and other circulatory changes. A heparin clearance test gave a flat curve of the type seen in the active stage of Buerger's disease. The patient stopped smoking, was given injections of sodium tetrathionate and later was kept under treatment with small doses of dicoumarin (3-3'-methylene bis [4-hydroxycoumarin]) given by mouth. There have been no fresh hemorrhages for some time, and central vision has returned to normal.

The cases of the 3 patients in whom the vascular condition seemed the only cause of the condition deserve a more detailed report.

A woman of 23 presented the picture of unilateral Eales' disease of several years' standing, with recent hemorrhages. The reactions to tuberculin were negative, as were the results of other examinations, except for the pressor tests, which revealed pronounced angiospasm. The patient was treated with barbiturates and tissue extract and had no other hemorrhages during observation. Vision, which was reduced to light perception, showed no improvement, but the other eye remained normal.

M. D., who was seen at the age of 12 years, presented retinal hemorrhages and bands of organizing connective tissue along the vessels about the disks. No evidence of tuberculosis or other infection was revealed, but pressor tests showed pronounced angiospasm, with a drop in temperature of 13 degrees (F.) following the nicotine test. Hemorrhages continued to occur for a time in spite of antispasmodic therapy, and it became impossible to see either fundus. These hemorrhages have finally ceased, and vision in one eye, after removal of the lens, which had become cataractous, is now 20/200. In the other eye a cataract has developed, and projection is faulty.

J. L., a boy of 8 years, was first seen when repeated hemorrhages had reduced his visual acuity to perception of light in the right eye and 6/200 in the left eye. He showed pronounced signs of peripheral angiospasm. The temperature of the toes was low and rose 10.5 (F.) degrees after nerve block. Oscillometric readings were low. Other examinations, including tuberculin tests, gave negative results. On treatment with neostigmine bromide, 7.5 mg. three times a day, he remained free from further hemorrhages for a year, with decided improvement in vision. One hemorrhage occurred at this time, but after treatment was resumed, vision continued to improve and at the end of two years was 20/200 in the right eye and 20/65 in the left eye.

A survey of the material shows that the situation is by no means as simple as that in central angiospastic retinopathy. It must be admitted that in periphlebitis retinae several factors may be responsible and that it is by no means easy to determine from the clinical picture which of these is the most likely one. In some cases, and perhaps in the majority, tuberculosis must be considered of causative importance. In other cases it must be said that no cause can be found. In a small group of cases, however, the factor of peripheral vascular disease seems to be of primary importance. Even in these cases the relation of spasm to the changes in the fundus it produces is by no means as definite as it is in central angiospastic retinopathy. It must be assumed that, as in Buerger's disease, chronic or repeated angiospasm produces organic changes, including, in addition to ischemia of the tissues supplied, stasis in the veins, with perivascular exudation and all the subsequent changes which one sees in the extremities. In fact, for this limited group of cases, the term thromboangiitis obliterans, employed by Marchesani, seems appropriate. Aside from spasm, there may be, as in the case previously mentioned, anomalies in the clotting mechanism, as shown by the heparin clearance and other tests. While the results of treatment are by no means so favorable as with central angiospastic retinopathy, the complete resistance of this much more serious condition to all forms of therapy in the past gives such results as have been reported in these few cases a certain interest.

It would seem that with such a serious condition, obviously involving the retinal vessels, examination of the peripheral vascular system should be included in the complete examination of every patient. Patients showing positive evidence of peripheral angiospasm, even when tuberculin reactions are also positive, may well be given the benefit of treatment designed to improve the peripheral circulation.

ARTERIOLAR SPASM OF THE RETINA

There are other ocular conditions in which peripheral angiospasm undoubtedly plays a part. Some of these, including spasm of the central retinal artery, have been discussed in the previous report. There is space here to speak of only one other condition, illustrated by a single case.

Mrs. K., a woman aged 53, was operated on for senile cataract of the left eye in December 1941. The usual preliminary tests revealed a normal status. After an uneventful intracapsular extraction, vision of 20/20 was obtained. After six months, however, vision began to fail, with no changes in the fundus except gradually progressive diminution in the size of the retinal arterioles. After two months of treatment with thiamine hydrochloride and vitamin B complex in large doses, vision was reduced to 20/80. At this time the patient was hospitalized for examination and treatment by Dr. Van Dellen. He reported a high degree of peripheral angiospasm, and treatment with neostigmine and tissue extract was begun. Vision began to improve slowly, and within four months it was 20/40. The arteries were still rather small. The right eye was operated on at this time, and a vascular condition similar to that in the left eye was revealed, with the best obtainable vision 20/65. Administration of neostigmine bromide was resumed, and two further courses of tissue extract were given. Vision slowly improved in both eyes, and fifteen months after the first operation it was 20/30 in the right eye and 20/20 in the left eye. The vessels of the right eye now showed a definite increase in size, being practically normal, while the disk, which had been pale, had improved slightly in color. The vessels of the left eye were still small, but larger than they had been at the height of the disturbance.

In this case, the only one of its kind in my experience, there seemed to be no doubt that arteriolar spasm was responsible for the loss of vision and that antispasmodic treatment affected the outcome favorably. The difficulty of judging the size of the retinal vessels in cases of aphakia is admitted, but when examination of the fundus reveals no other cause for loss of vision in such cases, or in other cases, and the retinal arterioles appear small, it is logical to advise examination of the peripheral vascular system.

CONCLUSIONS

The records of 23 patients present additional evidence that peripheral angiospasm is the cause of what has been described as central angiospastic retinopathy.

There is evidence that in a certain proportion of young adults with periphlebitis retinae and recurring hemorrhages in the vitreous peripheral vascular disease is the primary cause.

In a case of extreme attenuation of the retinal arterioles with marked peripheral angiospasm following operation for cataract antispasmodic treatment produced improvement.

In all cases in which the characteristics of these three syndromes are presented careful examination of the peripheral vascular system is indicated. In cases of other conditions in which it is desired to employ vasodilators, it would seem logical to advise such an examination before treatment is begun.

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DICKEY OPERATION FOR PTOSIS

RESULTS IN TWENTY-ONE PATIENTS AND THIRTY LIDS

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In 1935 Dickey conceived the idea of correcting ptosis, in cases with normal function of the superior rectus muscle, by using a sling of fascia lata through the middle third of that muscle and attaching it to the tarsus. This method was published in 1936 as a preliminary report.[1] Although the operation has been in use at the University of California since that time, no further cases were reported until Gifford and Puntenney [2] described their results in 5 cases in which they employed a modification of the Dickey procedure.

Many operations have been devised for ptosis. They may be divided into two principal classes: those employed when there is paralysis or paresis of the superior rectus muscle and those employed when this muscle has normal function. Here we are concerned with the latter.

The Blaskovics [3] operation has been used rather widely. In this procedure a piece of the tarsus is removed and the levator muscle, which has been resected from it, is brought forward and attached to the remaining portion of the tarsus. With complete ptosis this operation has been disappointing.

In 1897 Parinaud [4] and Motais [5] conceived the idea of substituting the middle third of a normally functioning superior rectus muscle for the paretic levator muscle. Since that time the basic principle of the Motais operation has been the one most universally used for correction of ptosis in the presence of a normally functioning superior rectus muscle. Shoemaker [6] modified the operation in 1907 by making an external incision, which gave a better exposure and permitted firmer suturing of the tongue of muscle to the tarsus. Kirby [7] also made minor changes in the operation.

There are several disadvantages to the original Motais operation and its modified forms. The strip of superior rectus muscle sutured to the tarsus may tear out. Even though Kirby [7] advised that it be immediately reattached by a second operation, this complication involves a risk, to be avoided if possible. Another disadvantage is the fact that, since the small strip is attached at one point only, there is a tendency to "tenting" or inverted V formation of the upper lid. The difficulty of performing this operation on small children is such that, in discussing the Motais operation, Bielschowsky [8] stated: ". . . it is not advisable to operate on young children because a child's superior rectus muscle is so small and delicate the suture may easily cut through it." The Motais operation also does not permit an adjustment of the degree of correction to make the lid conform in position to the lid on the other side. The superior rectus muscle is disturbed and injured, and its normal attachment is interfered with. In addition, the dissection entailed is considered difficult. Finally, according to Wheeler,[9] in rare instances, near the attachment of the superior rectus muscle to the upper lid, entropion may occur and the cilia rub on the cornea.

Because of these disadvantages various methods of employing the intact superior rectus muscle have been devised.

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Presented at the Forty-Eighth Annual Meeting of the American Academy of Ophthalmology and Otolaryngology, Section on Ophthalmology, Chicago, Oct. 11, 1943.

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3. Blaskovics, L.: Treatment of Ptosis, Arch. Ophth. **1**:672 (June) 1929.

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5. Motais, E.: Operation for Ptosis by Tarsal Grafting of a Tongue of the Tendon of the Right Superior Muscle, Ann. d'ocul. **118**:6 (July) 1897.

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7. Kirby, D. B.: Blepharoptosis: The Technique of Its Surgical Correction, Surg., Gynec. & Obst. **70**: 438, 1940.

8. Bielschowsky, A.: Lectures on Motor Anomalies of the Eyes: The Functional Neuroses; Etiology, Prognosis and Treatment of Ocular Paralysis, Arch. Ophth. **13**:751 (May) 1935.

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Wiener,[10] in 1928, advocated the operation suggested by Cannos and Arrangues, in which the levator muscle is severed almost 6 mm. from its tarsal attachment and sutured to the tendon of the superior rectus, so that the tarsus is attached to the latter muscle by means of a portion of the tendon of the levator. As Gifford and Puntenney [2] pointed out, this would "seem to produce an adhesion to the muscle too far from the lid border to accomplish the desired elevation of the lid in cases of complete ptosis."

In 1935 Trainor [11] presented an operation in which a strip of the upper edge of the tarsus is passed under the superior rectus muscle. With the lid everted, an incision is made 2 mm. from the superior edge of the tarsus and parallel with it for a distance of 7 to 10 mm. This strip, with the conjunctiva adherent, is then passed beneath the tendon of the superior rectus muscle and sutured back in place. The procedure has been described and illustrated in detail by Wiener and Alvis.[12] These authors recommended it as the simplest operation for ptosis. It does not allow, however, for an adjustment of position of the lid to balance that on the other side. It has the disadvantages pointed out by Spaeth [13] and Gifford and Puntenney [2] that it forms an undesirable adhesion in the upper cul-de-sac which interferes with the movement of the eye and that it buries an epithelial surface (the conjunctiva covering the strip of tarsus) beneath the superior rectus muscle.

In 1938 Wheeler [9] advocated correction of ptosis by attachment of strips of the orbicularis muscle to the superior rectus muscle. Through an external incision the dissection is carried through the orbicularis muscle, the tarso-orbital fascia, the levator muscle and Tenon's capsule, and the superior rectus muscle is picked up on a hook. Strips of orbicularis muscle are then dissected up from the tarsus, and the ends toward the canthi, which have been cut, are attached to the superior rectus muscle with fine catgut. This operation apparently does away with many objections to the Motais procedure, but, as Wheeler

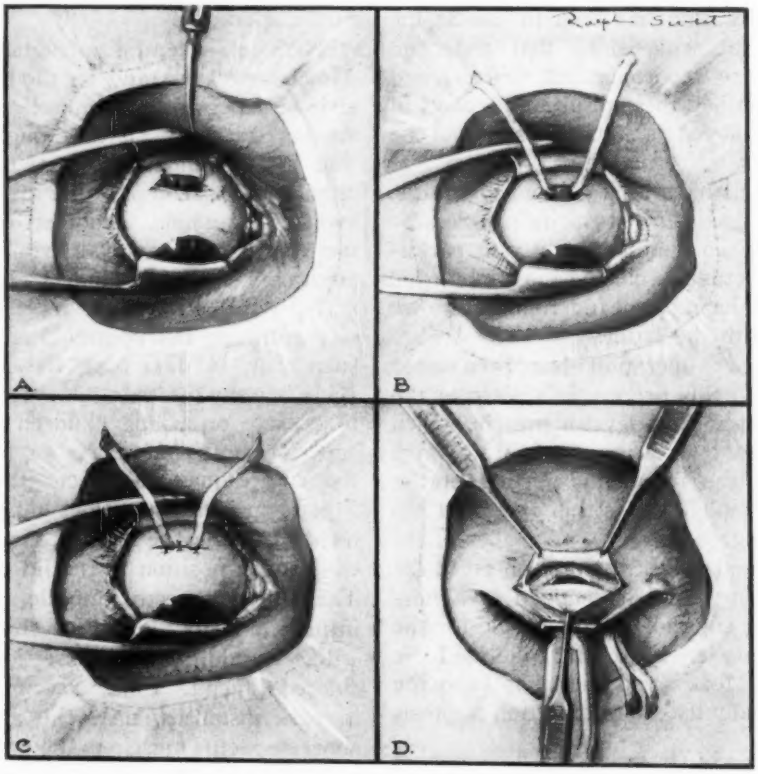

Fig. 1.—*A*, isolation of the superior rectus muscle; *B*, insertion of the strip of fascia lata under the central third of the tendon; *C*, conjunctiva and capsule sutured; *D*, tarsus exposed, showing 5 mm. incision made through the tendon of the levator muscle at the upper tarsal edge.

10. Wiener, M.: Correction of Defect Due to Third Nerve Paralysis, Arch. Ophth. **57**:597 (June) 1928.

11. Trainor, M. E.: Operation for Lid Ptosis, Tr. Sect. Ophth., A. M. A., 1935, p. 93.

12. Wiener, M., and Alvis, B.: Surgery of the Eye, Philadelphia, W. B. Saunders Company, 1939, p. 342.

13. Spaeth, E. B.: The Principles and Practice of Ophthalmic Surgery, Philadelphia, Lea & Febiger, 1939, p. 368.

himself pointed out, the dissection may be considered difficult.

Although there is no perfect substitute for a paralyzed muscle, we feel that the Dickey operation, based on our experience over a period of eight years, has given entirely satisfactory results and that it does away with most of the objections to other procedures. Spaeth,[14] in commenting on the Dickey operation, stated that it undoubtedly provides the firmest attachment any one can obtain between the superior rectus muscle and the tarsus.

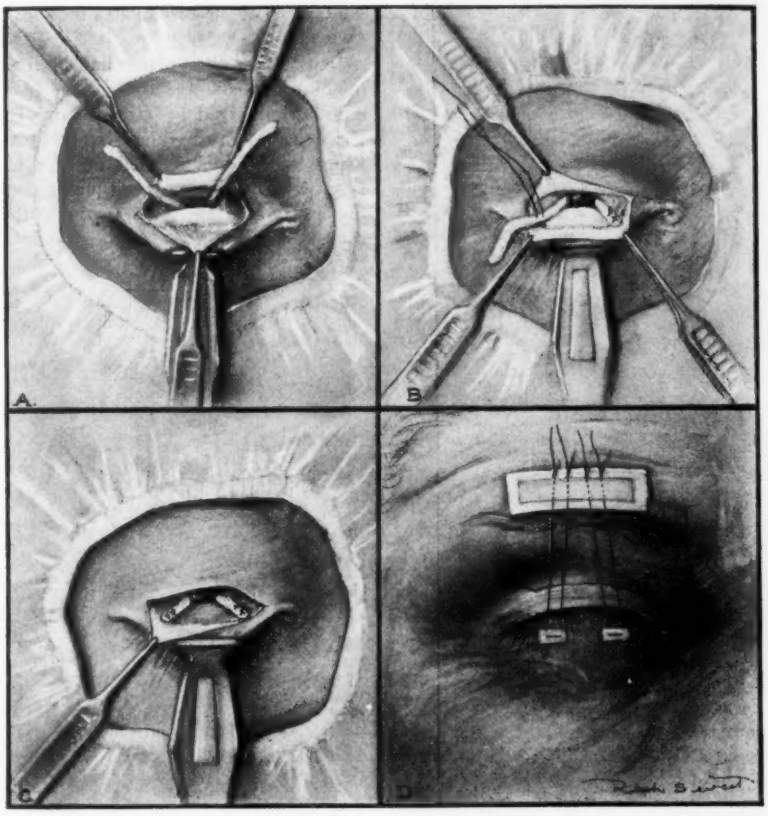

Fig. 2.—*A*, fascia brought through incision in the levator muscle; *B*, sutures through the tarsus and fascia, with the outer sutures tied; *C*, fascia lata sutured to the tarsus; *D*, lid sutures, inserted as advocated by Gifford and Puntenney.[2]

TECHNIC OF THE DICKEY OPERATION

The following technic is utilized: General anesthesia is employed, it having been used in all the cases in the present series. While the preliminary part of the operation is being carried out, a strip of fascia lata 8 to 10 cm. long and 8 mm. wide is obtained by a general or a plastic surgeon. To obtain the fascia a 2 cm. incision is made on the midlateral aspect of the thigh at the junction of the upper and the middle third. This incision is carried down through the subcutaneous tissue until the fascia lata is exposed. The fascia is bluntly separated from the overlying subcutaneous tissue, the stripping being carried toward the knee. Two short parallel incisions are made through the fascia in line of its fibers, about 8 mm. apart, and the fascia is cut between them. This free end of the fascial strip is passed through the loop of the fascial stripper and held taut by a heavy clamp. The stripper is forced down the thigh to the knee, where the fascial strip is cut across by the blade of the stripper. The subcutaneous tissue and the skin are closed in layers by interrupted sutures.

While the fascia is being obtained, an incision is made in the conjunctiva over the superior rectus muscle, and the muscle is exposed and picked up on a hook (fig. 1 *A*). The central third of the muscle is picked up and separated back a short distance. The fascia lata is folded with the muscle surfaces together. This gives it additional strength and also guards against its being cut through by the sutures.

The folded fascia lata is now passed beneath the central third of the muscle (fig. 1 *B*). The conjunctiva and Tenon's capsule over the lateral portions of the muscle are sutured with 0000 catgut. An additional conjunctival suture is placed over the central third of the muscle between the two folded bands of fascia, so that no raw surfaces remain. This does away with the possibility of conjunctival adhesions (fig. 1 *C*). The lid speculum is removed.

A lid clamp with a conjunctival plate (or a Jaeger lid spatula) is introduced under the lid. A horizontal incision, about 20 mm. in length, is made through the skin and the orbicularis muscle 8 mm. from the margin of the lid. The dissection is extended through the orbicularis muscle until the tarsus is exposed well down

14. Spaeth,[13] p. 367.

to the margin of the lid and upward to the upper edge of the tarsus and the tendon of the levator muscle.

At the midpoint of the upper edge of the exposed tarsus an incision 5 mm. in length is made through the tendon of the levator muscle into the conjunctival sac (fig. 1 *D*). The strips of fascia lata are now brought through this opening by forceps and pulled down over the tarsus (fig. 2 *A*).

A double-armed no. 0.009 white silk or linen suture is placed in the tarsus at the junction of the outer and

Fig. 3 (case 2).—L. V., aged 4 years, with bilateral congenital ptosis. *A*, appearance before operation; *B*, appearance after operation (note lid folds); *C*, position of lids in elevation, and *D*, lids closed.

the middle third and about 4 mm. from the margin of the lid. Both needles are then passed through the folded fascia and tied firmly, and the suture is cut. A second firm bite is taken in the tarsus with another double-armed suture, just below the site of the first suture, and the suture is passed through the fascia lata, tied and cut (fig. 2 *B*). This reenforces the first suture. Another double-armed suture is similarly placed at the junction of the middle and the inner third of the lid and about 4 mm. from the margin (fig. 2 *B*). The lid clamp is removed, and by traction on the fascial loop or sling the site of this suture is determined. The point chosen for this mattress suture will determine the effect obtained and therefore should be carefully estimated. Originally Dickey advised that the point be chosen that will lift the margin of the lid to a point 3 mm. below the limbus. More recently we have selected a point 2 mm. from the limbus in most cases, while Gifford and Puntenney found that they obtained satisfactory results with the lid margin 1 mm. from the limbus. The suture is now introduced through the fascia at the chosen point and tied lightly. The position is inspected, and if it is satisfactory, the suture is tied tightly. Another mattress suture is placed just below this suture, introduced through the fascia and tied. The sutures are cut, and the excess fascia lata is trimmed off (fig. 2 *C*).

The position of the lid is now inspected to be certain that the margin is horizontal. If one side of the border is higher than the other, the fascia is adjusted at the point where it passes through the middle third of the superior rectus muscle. In case 19, with partial ptosis, in which the outer half of the lid drooped more than the inner half, the fascia was adjusted to compensate for this difference.

The cutaneous incision is closed with a continuous subcuticular suture, the white fascia sutures being buried. The fibers of the orbicularis muscle fall together of their own accord.

In the past the cornea has been protected by the use of ointment or a moist chamber. We feel that the method employed by Gifford and Puntenney (based on Friedenwald's procedure) is probably better and are now using it. By this method the "protection of the cornea is secured by passing two double-armed sutures through the lower lid and out through the lid border. The sutures are attached to the brow on adhesive tape so

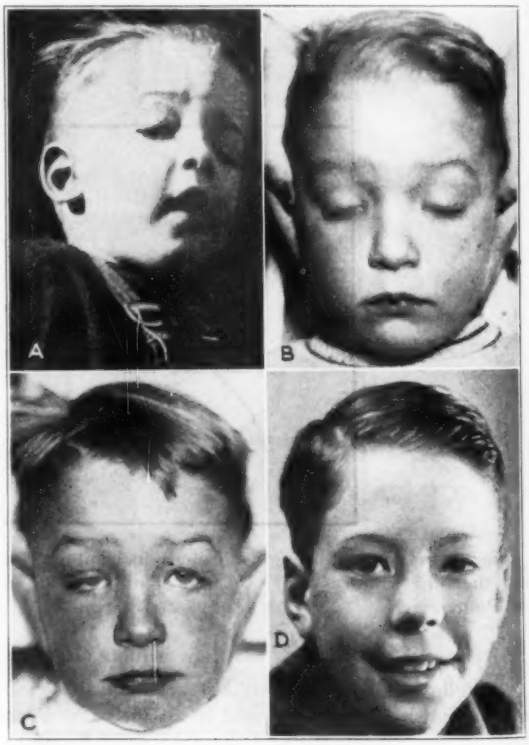

Fig. 4 (case 3).—M. R., aged 2½ years, with bilateral congenital ptosis. *A* and *B*, before operation; *C*, six weeks after operation, and *D*, three years after operation.

as to pull the lower lid up to the new level of the upper lid" [2] (fig. 2 *D*).

The subcuticular suture is removed on the sixth day. The sutures of the lower lid, which may be relaxed by removal of the tape for dressings, renewed every second day, are also taken out on the sixth day.

REPORT OF CASES

The following case reports from the University of California Medical School show the results obtained with the Dickey operation for ptosis. In this series 30 lids, in 21 patients, were operated on by various members of the staff.

CASE 1.—G. C., a boy aged 20 months, was brought to the clinic with the history of bilateral ptosis since birth. The drooping of the lids was so extreme that the patient was compelled to throw his head back in order to see. Operation on the right lid was done on March 11, 1935, and at this time sufficient fascia was obtained for operation on the other side. This fascia was preserved in alcohol and used for the left eye, when it was operated on six weeks later. The result obtained in the right eye was excellent, while the operation on the left eye resulted in complete failure, the fascia, as observed at a second operation, being entirely absorbed. Six months later the left eye was operated on again, without difficulty, and an excellent result was obtained. This was Dickey's first operation, and no attempt has since been made to use preserved fascia.

CASE 2.—L. V., a boy aged 4 years, was brought to the clinic Aug. 19, 1935 because of inability to open his eyes. Except for bilateral congenital ptosis the eyes were normal. On August 26 both lids were operated on, and an excellent result was obtained in both eyes (fig. 3).

CASE 3.—M. R., a boy aged 2½ years, was seen in January 1936 because of bilateral congenital ptosis. On Feb. 4, 1936 both lids were operated on, with an excellent result. A few areas of corneal staining were present for a short time after operation, but these cleared, without corneal scarring (fig. 4).

CASE 4.—D. T., a boy aged 9 years, presented bilateral ptosis, which was almost complete in the left eye. Operation was performed on the right lid on June 9, 1936 and on the left lid on Aug. 13, 1937. A good result was obtained, the position of the lid of each eye being 1 mm. above the upper pupillary border.

CASE 5.—H. L., a woman aged 20, gave a history of progressively increasing ptosis of both lids over a period of five years. The condition had apparently been stationary for the preceding year. After a medical examination, the results of which were essentially without significance, an operation was performed on the left lid on March 23, 1937, with a good result. The patient had vertical diplopia, which persisted until operation was carried out on the right lid, on Oct. 27, 1937. An excellent result was obtained, with good folds in both lids.

CASE 6.—D. T., a boy aged 5 years, presented bilateral congenital ptosis, more pronounced on the right side. Operation was performed on the right lid on June 18, 1937 and on the left lid on Aug. 13, 1937, with excellent results.

CASE 7.—C. H., a boy aged 15, presented congenital ptosis of the left lid, and operation was performed on June 4, 1937. After the surgical procedure there was an overcorrection of about 1 mm. The patient had diplopia on extreme elevation of the lids. He was so well satisfied with the result of operation that he would not consent to further surgical treatment.

CASE 8.—B. L., a man aged 21, had bilateral ptosis and epicanthus, for which operation had been carried out elsewhere two years before the present entrance. A modified Motais operation had been done on both sides. The patient stated that his condition was worse after the surgical procedure. In spite of slight weakness of the left superior rectus muscle, it was decided to perform a bilateral Dickey operation, which was carried out on June 15, 1938. At the time of operation scar tissue was present over the superior rectus muscle, and the tongue used in the Motais procedure appeared to have retracted. Little difficulty was encountered during the operation, and the patient obtained an excellent cosmetic result. He had occasional diplopia during the year and a half that he was under observation. This, however, was not troublesome enough to lead him to consent to further surgical intervention.

Fig. 5 (case 15).—N. G., aged 23, with congenital ptosis; internal strabismus of the left eye, with a 25 degree arc; some weakness of the left superior rectus muscle, and amblyopia of the left eye. Two previous operations had been performed for ptosis—probably shortening of the levator muscle and the Motais procedure. *A*, appearance after two previous operations; *B*, appearance after the Dickey operation; *C*, position of the lid in elevation. There was no diplopia, as a result of amblyopia and suppression.

CASE 9.—A. S., a boy aged 9 years, had an operation on Aug. 7, 1937 for bilateral congenital ptosis, with satisfactory results.

CASE 10.—T. R., a boy aged 4 years, had an operation on Sept. 3, 1937 for complete congenital ptosis of the left lid. The result was excellent. A year later the mother stated that the psychologic effect on the child was "amazing."

CASE 11.—S. J., a girl aged 13 months, had congenital ptosis of the right lid, for which operation was

performed on Oct. 28, 1937. The result was entirely satisfactory. This patient is the youngest on whom the operation has been done. No particular difficulties were involved as a result of the small size of the patient.

Case 12.—B. M. A., a boy aged 16, had congenital ptosis of the right lid. His grandfather had a similar condition. Operation was performed on the right lid on Jan. 31, 1938, with excellent result. Seven months later he returned with a definite gray band extending across the cornea and running through the lower third of the pupil. The lids were sutured together for three weeks, and at the end of this time there was no staining. When the patient was seen six months later, the condition of the eye was quiet, but a fine linear scar ran across the lower third of the pupil.

Fig. 6 (case 19).—C. M., aged 8 years, with partial ptosis of the right lid from birth. *A*, appearance before the Dickey operation on the right eye; *B*, appearance after operation. A slight overcorrection of the inner half emphasizes the necessity of careful adjustment of fascia.

Case 13.—F. C., a boy aged 9 years, had partial congenital ptosis of the left lid. The margin of the lid lay at the center of the pupil. Operation was performed on Jan. 4, 1938, the lid margin being placed at the same level as that of the fellow eye. The result was excellent. The patient had diplopia on extreme elevation of the lid. This was not troublesome but was still present eighteen months later.

Case 14.—H. G., a boy aged 9 years, had congenital ptosis of the right lid, for which operation was performed on Feb. 20, 1940, with satisfactory results.

Case 15.—N. G., a woman aged 23, had complete ptosis of the left lid, associated with an internal strabismus of 25 degrees. There was hyperphoria on the right side, together with some weakness of the left superior rectus muscle. The left eye was amblyopic. Before coming to the clinic the patient had had an operation for the strabismus and two operations for the ptosis. As well as could be determined, the first operation for ptosis had been shortening of the superior rectus muscle, with attachment of the levator muscle. The second operation for ptosis was the Motais procedure. Both operations had failed to correct the defect, so that when we first saw her she had complete ptosis of the left lid (fig. 5 *A*). It was decided that a Dickey operation would offer the best cosmetic results, even though there was some weakness of the superior rectus muscle, together with hypophoria. Since the eye was amblyopic there was no fear of diplopia.

This operation was performed on July 2, 1940. Because of the scar tissue from previous operations, the dissection was a little more tedious but not difficult. On April 29, 1941, a second operation for the strabismus was done. Cosmetically the result was extremely satisfactory, particularly in view of the two previous failures. When the eye is in the primary position there are a little hypophoria, a slight drooping of the lid and some fulness at the outer corner (fig. 5 *B*). While the upward motion of the left eye is somewhat limited, owing to the weakness of the superior rectus muscle, the lid follows the eyeball up, so that there is no great cosmetic disfigurement (fig. 5 *C*). The left eye being amblyopic, there has been no diplopia. While the end result is not as perfect as in the cases of uncomplicated ptosis, we feel that in view of the existing circumstances the operation can be called successful.

Case 16.—D. C., a boy aged 4 years, had bilateral congenital ptosis, for which an operation was performed on both sides. The results were satisfactory, although the left lid was 1 mm. lower than the right, owing to a slight undercorrection.

Case 17.—T. P., a boy aged 3 years, had complete congenital ptosis on the right side, for which operation was performed on Feb. 7, 1941, with satisfactory results. After operation some difficulty was encountered in trying to prevent the cornea from drying out, and in spite of all efforts a small corneal infiltrate and resultant scar developed.

Case 18.—L. K., a youth aged 17, had bilateral congenital ptosis. Operation was performed on the right side on June 11, 1941 and on the left side on May 1, 1942, with excellent results in both procedures.

Case 19.—C. M., a boy aged 8 years, had partial ptosis of the right lid, the margin of which crossed the middle of the pupil. In addition, the outer part of the lid was considerably lower than the inner part. Operation was performed on May 26, 1942, particular care being taken to see that the outer and the inner half of the lid were on the same level. The result was excellent, the position of the lid being at the same level as that of the other eye (fig. 6).

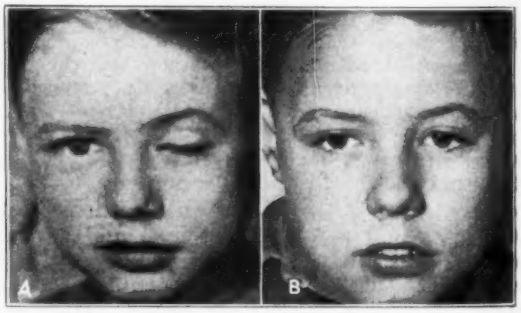

Fig. 7 (case 21).—B. F., aged 10 years, with congenital ptosis on the left side. *A*, before Dickey operation; *B*, after the operation.

Case 20.—F. M., a boy aged 8 years, had either congenital or obstetric ptosis of the right side, for which operation was performed on July 18, 1942, with excellent results.

Case 21.—B. F., a boy aged 10 years, had congenital ptosis on the left side (fig. 7 *A*). A Dickey operation was done on Aug. 4, 1942, with a satisfactory result, the left lid now being at the same level as the right (fig. 7 *B*).

COMMENT

This series presents 21 cases in which the ptosis was corrected by the Dickey operation, which was performed on 30 lids. Of the patients, 18 were males and 3 females.

The youngest patient was a girl of 13 months (case 11). In view of the difficulty of doing a Motais operation on a patient of this age, it is interesting to note that no complications were encountered and that the result was excellent. The oldest patient was a woman of 23 (case 15), whose case warrants special comment.

In this series there was 1 instance of outright failure (case 1), probably due to the fact that preserved fascia was used. In 2 instances (cases 15 and 16) there was slight undercorrection. In case 15, in which the lid had twice been operated on, without success, there was a good deal of scar tissue, which made the dissection a little more difficult; in addition, a fulness of the outer half of the lid tended to emphasize the undercorrection (fig. 5 *B*). In 1 instance (case 7) there was an overcorrection of about 1 mm.

In 3 cases (cases 1, 8 and 15) previous operations for the ptosis had been performed, without success. In 2 instances the Motais procedure had been used. Aside from the slight inconvenience of dissecting through scar tissue, no difficulties were encountered in the second operation in these cases, and good results were obtained in all of them.

In 3 cases corneal involvement followed surgical correction, a small corneal scar resulting in 2 cases. The corneal reaction occurred during the early convalescent period. This proportion of cases seems rather high, and we feel that the use of the two double-armed sutures through the lower lid, which Gifford and Puntenney [2] suggested and which we are now using, will materially reduce the occurrence of this complication.

It is noteworthy that in none of the cases was there any tendency to "tenting," or an inverted V formation of the palpebral fissure. In addition, in almost every case the lid folds had a normal configuration (figs. 3, 4, 6 and 7).

In 4 cases there was diplopia. In case 5 this disappeared after operation on the other eye. In cases 7 and 13 diplopia was evident only on extreme elevation of the lid. This diplopia was not sufficient to be troublesome and annoyed the patient far less than the ptosis. In case 8 slight weakness of the superior rectus muscle, diagnosed before operation, accounted for the diplopia and was not sufficient to be annoying. In case 15 there was also slight weakness of the superior rectus muscle. Amblyopia in that eye, with suppression, prevented diplopia. Case 8 emphasizes the necessity of careful study of the superior rectus muscle and the eye before operation is contemplated.

Slight weakness of the superior rectus muscle is not a contraindication to the Dickey operation if there is amblyopia or suppression. Also, if the paresis is mild and will cause diplopia only on extreme elevation of the eye, the Dickey procedure is preferable to an operation in which the lid is fixed and does not follow the movement of the eyeball. In the Dickey operation the lid is attached by the fascial sling to the tendinous insertion of the muscle, so that the entire superior rectus muscle aids in holding up the lid; consequently, the presence of slight weakness does not materially alter the action of the muscle. In the Motais procedure, in which the effect is produced by only a portion of the muscle, any weakness would be exaggerated.

In a case in which operation was performed elsewhere diplopia was so marked because of paresis of the superior rectus muscle that it became necessary to undo the results of the operation and restore the ptosis. It is noteworthy that such a procedure is simple. The operator reaches into the upper conjunctival sac with a small muscle hook, such as that used in the O'Connor operation and easily picks up the strips of fascia on either side and cuts them with tenotomy scissors, thus restoring the former ptosis.

The fact that obtaining the fascia lata necessitates an additional surgical procedure has brought forth some criticism. Ptosis is such a disfiguring and distressing condition that any aid obtainable in overcoming it seems justifiable. The obtaining of the fascia is not difficult, and the scar on the thigh is a small one. In none of the cases in which the fascia was obtained was any postoperative complication contingent on its removal. In view of the many advantages of the Dickey operation, we do not feel that the objection to the additional surgical procedure required in obtaining the fascia is justified.

Gifford and Puntenney [2] modified the Dickey operation in that they operated entirely through a cutaneous incision and passed the fascial sling under the entire superior rectus muscle. We can see no real disadvantage to these procedures. We have felt that for the average operator there is less difficulty in isolating the superior rectus muscle through the conjunctival incision. After the fascia has been passed through the central third of the muscle, the conjunctiva is closed on either side right up to the fascia. In addition, another suture brings the conjunctiva together between the two bands of fascia (fig. 1 *C*). The conjunctiva is closed with 0000 catgut, so that it is unnecessary to remove sutures. To date, we have not seen adhesions form in the conjunctival

sac, and in a case previously noted cutting of the bands of fascia restored the ptosis. Gifford and Puntenney apparently limited the Dickey operation to cases of complete ptosis. We have used the operation with excellent results in cases of partial ptosis in which an attempt is made to elevate the lid to the level of that of the fellow eye (cases 13 and 19; fig. 6). In these cases, particularly, it is advisable not to destroy what action the levator may have. Consequently, it seems advantageous to make only a small opening through the tendon at the upper tarsal edge through which the bands of fascia can be passed (fig. 1 *D*), rather than to sever the tendon completely by using a cutaneous incision for the entire operation. Thus, in the event of failure of the operation, the partial ptosis would be no worse than it was before operation. In case 8 a Motais operation had been done elsewhere for partial ptosis. As well as could be determined, it was done entirely through a cutaneous incision. The operation was a failure, with the result, the patient stated, that the ptosis was worse than it had been before surgical intervention.

We have felt that putting the fascial sling through the central third of the muscle allows for a little better adjustment, especially in such cases as case 20, in which one side of the lid was lower than the other. It would seem that in cases of this kind there would be less tendency for the fascia to slip than when it passes beneath the entire muscle.

We have also found that placing the border of the lid 3 mm. below the limbus makes the margin a little low; we therefore have been placing it 2 mm. below. The final decision as to where the border of the lid will be placed depends to a certain extent on the position of the lid in the normal eye. It should be emphasized that the position of the normal lid should be carefully studied before operation is attempted.

SUMMARY

The Dickey operation for ptosis has been used at the University of California for eight years. During this time 30 lids have been operated on in 21 patients, with satisfactory results.

The operation can be used with small children, the youngest patient in this series being a 13 month old child.

In only 3 cases was there permanent diplopia; in 2 of these it was present only on extreme elevation of the lid, and in the third, only at times.

Three lids previously operated on by other methods without success were corrected without great difficulty.

In addition to its use in the presence of a normally functioning superior rectus muscle, the operation can be employed to advantage in cases of slight weakness of the superior rectus muscle in which the corresponding eye is amblyopic or suppresses the image. In these cases the cosmetic result is better than when the position of the lid remains fixed, and with amblyopia or suppression there is no fear of troublesome diplopia.

Owing to the two point suspension, there is no tendency to the inverted V formation of the lid, and the folds of skin show the normal conformation.

The operation permits adjustment of the position of the lid to conform with that of the other side.

The operation has been found satisfactory in cases of bilateral complete ptosis, unilateral complete ptosis and partial ptosis when the action of the superior rectus muscle is normal.

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ROLE OF SARCOIDOSIS AND OF BRUCELLOSIS IN UVEITIS

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In a previous report on the etiology of uveitis [1] we stated that the importance of sarcoid and of brucellosis could not then be properly evaluated. The significance of these conditions as causes of uveitis was not appreciated until late in this previous study, and search for evidence of these diseases had not been routinely made. The previous study included patients with uveitis admitted to the Wilmer Ophthalmological Institute up to July 1, 1939. A survey of the patients with uveitis admitted from July 1, 1939 to June 30, 1943 revealed that during this period exactly 200 were completely studied, with the idea of establishing the cause of the uveal disease. Included in the general study were searches for any evidence of sarcoidosis or of brucellosis. It is the purpose of this paper to present the results of the etiologic study of these 200 patients and to discuss the general problems of sarcoidosis and brucellosis as related to uveitis.

The routine diagnostic procedures in the study of these patients were as follows: (1) complete ophthalmic examination; (2) taking of the medical history and general physical examination; (3) routine urinalysis and routine studies of the cellular and chemical constituents of the blood; (4) serologic tests for syphilis; (5) quantitative intracutaneous tests for hypersensitivity to tuberculin, (6) roentgenologic examination of the chest; (7) routine search for foci of infection in the nose, throat, accessory nasal sinuses, teeth and genitourinary tract; (8) gonococcus complement fixation tests; (9) agglutination tests for brucellosis, and for some patients complement fixation tests for the organism, and estimation of the opsonocytophagic index, and (10) when sarcoidosis was suspected, biopsy of a lymph gland or cutaneous nodule, estimations of the albumin and globulin contents of the serum and, in many cases, roentgenographic examination of the hands and feet.

The histories of only 27 of the entire series of 200 patients did not contain these minimal data. These were patients with proved syphilis, sarcoidosis, herpes simplex or gonococcic arthritis. For all of these 27 patients the diagnosis was so clear from the examinations made that irrelevant studies were omitted. In addition to the aforementioned minimal diagnostic procedures, special bacteriologic examinations, sensitivity studies and examinations of the spinal fluid were carried out when indicated. Frei tests for lymphogranuloma venereum were made on a number of patients, but in no instance did such tests appear of diagnostic value. Protection tests for Toxoplasma were not made until 1943.

In this study the criteria for an absolute or a presumptive diagnosis of tuberculosis, syphilis, a focus of infection, gonorrhea and miscellaneous diseases as etiologic factors are exactly those outlined and described in our previous paper. The criterion for the diagnosis of sarcoidosis as the etiologic factor is the histologic demonstration of lesions of the disease in an excised gland or a cutaneous nodule. There is no "presumptive" diagnosis of sarcoidosis. The criteria for the diagnosis of infection with Brucella as the etiologic factor are the elimination of other obvious causes for the uveal disease and the presence of a positive serologic reaction or evidence of sensitivity to such an infection. It thus follows that all the diagnoses of brucellosis as the etiologic factor are in a sense presumptive.

One third of the 200 patients were from private practice, and two thirds were from the public wards. No strictly outpatients were included in this series. With only an occasional exception, all the patients were examined and studied under the direction of one of us.

The results of the etiologic study of these 200 patients are shown in table 1.

As in the former study, the patients reported on here are divided into two groups: Group 1 consists of 102 patients for whom the results of the study were so conclusive that an absolute diagnosis appeared justified, and group 2, of 98 patients for whom the accumulated evidence was not conclusive. For 76 of these patients evidence was sufficient to permit a presumptive diagnosis, but for 22 patients the study was either totally

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Read at the Forty-Eighth Annual Session of the American Academy of Ophthalmology and Otolaryngology, Chicago, Oct. 13, 1943.

1. Guyton, J. S., and Woods, A. C.: Etiology of Uveitis: A Clinical Study of Five Hundred and Sixty-Two Cases, Arch. Ophth. **26**:983 (Dec.) 1941.

unproductive or so inconclusive that no deduction could be drawn as to the cause of the uveitis. The etiologic factors for 22 patients are listed as "undetermined." For purposes of comparison, the table giving the results reported in our first paper [1] is reproduced here (table 2).

Analysis of table 1 and a comparison with the results of the former study, shown in table 2, yield interesting observations. The figure for tuberculosis in table 1 is 41 per cent, and in table 2, 49.7 per cent. In our first series (table 2) the cases of all but 3 patients with sarcoidosis were undoubtedly included under tuberculosis. If the patients with sarcoidosis are added to those with tuberculosis, the incidence for the two diseases is 48.5 per cent in the present study, as compared with 50.2 per cent in the former study. The incidence of syphilis in this study, 14 per cent, is slightly higher than that in the first study, but this increase is accounted for by the admittance to the wards of a few patients with known syphilis for hyperpyrexia therapy. The figures for gonorrhea as an etiologic agent are statistically comparable in the two series—6.5 and 4.6 per cent. Rheumatoid arthritis is listed in this series as a separate etiologic factor, rather than being included under "nongranulomatous systemic infections." This is done in order to make special note of what appears to us to be a definite clinical entity, recurrent serous iritis associated with rheumatoid arthritis and, usually, a specific hypersensitivity to certain streptococcus antigens.

One striking difference between the figures now reported (table 1) and those previously given (table 2) lies in the number of patients whose uveitis was attributed to a focus of infection. In this series the ocular condition of only 6 per cent of the total number of patients was attributed to focal infection. Even if the patients whose disease was attributed to brucellosis were included under "foci of infection," the total would be only 13.5 per cent. This is in contrast to a total of 26.1 per cent in our first series. This difference illustrates clearly our growing disbelief in the importance of focal infection as a frequent cause of uveal disease and the unwillingness of our consultants to lay stress on trivial and minor foci of infection which appear clinically unrelated to the ocular condition. Consequently, the incidence of uveitis of undetermined origin is much higher in this series.

TABLE 1.—*Etiologic Factors of Uveitis, Either Definite or Presumptive, in Present Series of Two Hundred Patients*

Etiologic Factor	Group 1: 102 Patients with Definite Evidence of Etiologic Factor		Group 2: 98 Patients with Presumptive Evidence of Etiologic Factor		Total: 200 Patients	
	No. of Patients	Percentage *	No. of Patients	Percentage *	No. of Patients	Percentage
Tuberculosis	39	19.5	43	21.5	82	41.0
Syphilis	24	12.0	4	2.0	28	14.0
Sarcoidosis	15	7.5	0	0.0	15	7.5
Brucellosis	0	0.0	15	7.5	15	7.5
Foci of infection	4	2.0	8	4.0	12	6.0
Rheumatoid arthritis	5	2.5	0	0.0	5	2.5
Gonorrhea	7	3.5	6	3.0	13	6.5
Miscellaneous	8	4.0	0	0.0	8	4.0
Undetermined origin †	0	0.0	22	11.0	22	11.0
	102	51.0	98	49.0	200	100.0

* Percentages are given on the basis of the total series of 200 cases on which this report is based.
† The 22 cases of uveitis of undetermined origin consist of 9 cases of granulomatous uveitis and 13 cases of nongranulomatous uveitis.

TABLE 2.—*Etiologic Factor: Diagnosis, Either Definite or Presumptive, for 562 Patients with Uveitis*

Etiologic Factor	Group 1: 244 Patients with Definite Evidence of Etiologic Factor		Group 2: 318 Patients with Presumptive Evidence of Etiologic Factor		Total: 562 Patients	
	No. of Patients	Percentage	No. of Patients	Percentage	No. of Patients	Percentage
Tuberculosis	132	23.5	147	26.1	279	49.7
Syphilis	45	8.0	14	2.5	59	10.5
Sarcoid	3	0.5	0	0.0	3	0.5
Brucellosis	1	0.2	1	0.2	2	0.4
Foci of infection	31	5.5	116	20.6	147	26.1
Gonorrhea	10	1.8	16	2.8	26	4.6
Nongranulomatous systemic disease	14	2.5	19	3.4	33	5.9
Metabolic disease	0	0.0	3	0.5	3	0.5
Miscellaneous	8	1.4	2	0.4	10	1.8
Total	244	43.4	318	56.5	562	100.0

COMMENT

Sarcoidosis.—The term "sarcoid" was first used in 1899 by the Norwegian dermatologist Boeck,[2] who described the cutaneous manifestations of the disease. The changes he described were later shown to be similar to those described in 1889 by Besnier[3] under the name of "lupus pernio." Boeck later changed his first concept of the relation of these cutaneous changes to sarcoma and termed the condition "benign miliary lupoid." In 1914 the modern concept of this disease was stated by Schaumann,[4] who recognized the disease to be a chronic granulomatous disorder of uncertain course and spotty distribution, relatively benign, capable of affecting any organ in the body but with considerable predilection for the reticuloendothelial system. He termed the disease "benign lymphogranulomatosis." The disease is variously known under these, and other, appellations and is associated with the names of these three authors. The most popular name is the misnomer applied by Boeck —"sarcoid." Within the last few years this disease has received widespread attention, and a number of excellent reviews have appeared, notable among which are the reports of Scott[5] (1938), Harrell[6] (1940) and Longcope[7] (1941).

In general, sarcoidosis is a relatively benign, chronic disease, occasionally punctuated with acute exacerbations. The constitutional symptoms are slight, and while fever may be present in the early stages in some cases, more frequently it is entirely absent. The clinical symptoms produced by sarcoidosis are usually the result of local mechanical obstruction, with consequent irritation and interference with function, rather than of general toxemia or a systemic reaction. A peculiar laboratory observation reported in about 90 per cent of patients with sarcoidosis is a disturbance in the albumin-globulin ratio of the blood serum, due to an elevation of the globulin. There is no leukocytosis, but sometimes moderate eosinophilia is present. The sedimentation rate is usually increased, as is the calcium content of the blood. Patients with sarcoidosis usually, but not always, show a remarkable anergy to tuberculin, often failing to show any reaction to such large doses as 1, or even 10, mg. of old tuberculin injected intracutaneously.

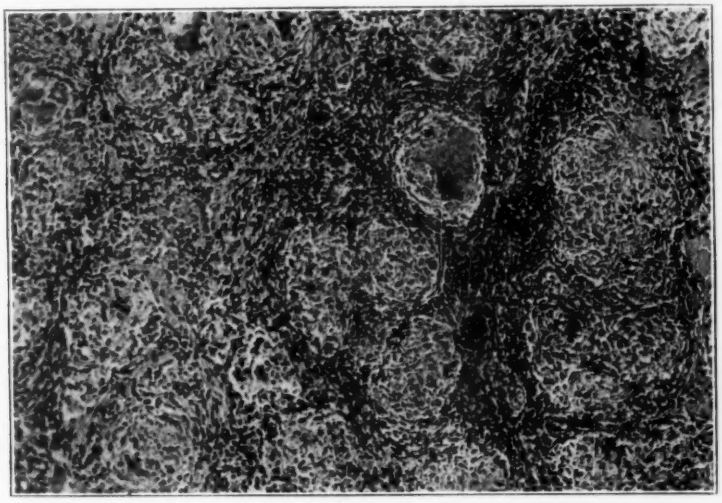

Fig. 1.—Photomicrograph of a lymph node in a case of sarcoidosis.

The characteristic pathologic lesions of sarcoidosis are tubercle-like masses of epithelioid cells, usually without any surrounding zone of inflammatory cells, or at best a scanty peripheral sprinkling of lymphocytes (fig. 1). There is

2. Boeck, C.: Multiple Benign Sarcoid of Skin, J. Cutan. & Genito-Urin. Dis. **17**:543, 1899.

3. Besnier, E.: Lupus pernio de la face: Synovites fungueuses (scrofulotuberculeuses) symetriques des extremites superieures, Ann. de dermat. et syph. **10**:333, 1889.

4. Schaumann, J.: Etude sur le lupus pernio et ses rapports avec les sarcoides et la tuberculose, Ann. de dermat. et syph. **6**:357, 1916-1917.

5. Scott, R. B.: The Sarcoidosis of Boeck, Brit. M. J. **2**:777, 1938.

6. Harrell, G. T.: Generalized Sarcoidosis of Boeck: A Clinical Review of Eleven Cases with Studies of the Blood and the Etiologic Factors, Arch. Int. Med. **65**: 1003 (May) 1940.

7. Longcope, W. T.: Sarcoidosis, or Besnier-Boeck-Schaumann Disease, J. A. M. A. **117**:1321 (Oct. 18) 1941.

rarely any evidence of caseation or necrosis. These tubercles usually, but not always, contain giant cells. In 20 per cent of cases peculiar, hematoxylin-staining, usually doubly refractive inclusions, known as Schaumann bodies, are seen in the giant cells. If Schaumann bodies are not present, it is impossible to differentiate lesions of sarcoidosis histologically from the "hard" tubercles of tuberculosis. In sarcoidosis these individual clusters of cells remain small but usually become numerous, forming macroscopic nodules with a proliferative tendency. They may remain unchanged for months or years, usually healing with scanty fibrosis and hyalinization.

While the nodules of sarcoidosis occur diffusely throughout the body, they have a decided predilection for the reticuloendothelial system. Generalized or spotty glandular enlargement is frequent, and the lymph glands practically always show the characteristic microscopic lesion. Roentgenologically visible lesions of the lungs are present in the majority of cases, principally in the form of diffuse infiltration, more noticeable at the hilus and in the lower portion of the lungs. Nodules of the skin of varying size and consistency occur in about one-half the cases. The liver and spleen are likewise involved in about 50 per cent of cases of this disease. Less frequent, but characteristic, manifestations of the disease are the rarefaction of the phalanges of the hands and feet, peculiar punched-out areas visible on roentgenographic examination. Nerve palsies, especially of the facial nerve, occur in the uveoparotid type of the disease. Lesions of other structures, the heart, muscles or meninges, are not often evident clinically but are frequently observed on microscopic examinations. It should be emphasized that while the lesions may be widespread, the distribution is spotty, and the individual patient usually shows only a few of the various clinical manifestations of the disease.

The cause of sarcoidosis is unknown. The elevation of the serum globulin, the antibody-containing protein of the blood serum, suggests that the disease may be the result of an actual infection, but no infectious agent, either virus or bacterial, has ever been isolated. Because of the similarity of the pathologic lesions to hard tubercles and the fact that about 10 per cent of patients with sarcoidosis later have frank tuberculosis, the relationship of sarcoidosis to tuberculosis has repeatedly been suggested, including the possibility that sarcoidosis may be due to an attenuated human strain of the tubercle bacillus or to some similar mycobacterium, such as the avian strain. However, the characteristic caseation and necrosis of tuberculosis are rarely seen in lesions of sarcoidosis; all experiments on transmission and inoculation have been fruitless, and anergy, rather than hypersensitivity, to tuberculin and various strains of mycobacteria is the general rule.[8] The fact that some patients with sarcoidosis later have tuberculosis is due probably to the widespread involvement of the lungs by sarcoidosis and consequent impairment of function and resistance to tuberculosis.

The presumptive diagnosis of sarcoidosis depends on the demonstration of the clinical manifestations of the disease, the cutaneous changes, the pulmonary infiltration, the rarefactions of the bones of the hands and feet, the elevation of the globulin in the serum, and the frequent anergy to tuberculin. Williams and Nickerson [9] demonstrated that sarcoid material taken for biopsy when injected beneath the skin of patients with sarcoidosis produces typical nodules of the disease. Later investigators demonstrated that any inert material, such as killed staphylococci and pigment granules, would produce the same effect. This reaction is of some diagnostic value in Negro patients. The absolute and final diagnosis of sarcoidosis must depend on the demonstration of characteristic lesions in biopsy material, usually a lymph gland.

The first report of ocular involvement associated with sarcoidosis was made by Schumacher,[10] who observed iritis in a recognized case of sarcoidosis. Within the next decade a sprinkling of such cases was reported. Ophthalmologic interest in sarcoidosis was stimulated by the almost simultaneous reports of Bruins Slot,[11] in 1936; of Longcope and Pierson,[12] in 1937, and of Pautrier,[13] in 1938, all of whom identified sarcoidosis with "uveoparotid fever," a syndrome first described by Heerfordt,[14] in 1909. Prior to

8. Brooke, W. S., and Day, R.: Skin Sensitivity to Mycobacterial Tuberculins in Sarcoidosis, Bull. Johns Hopkins Hosp. **72**:101, 1943.

9. Williams, R. H., and Nickerson, D. A.: Skin Reactions in Sarcoid, Proc. Soc. Exper. Biol. & Med. **33**:403, 1935.

10. Schumacher: Fall von beiderseitiger Iridocyclitis chronica bei Boeckschem multiplem benignen Sarkoid, München. med. Wchnschr. **56**:2664, 1909.

11. Bruins Slot, W. J.: Besnier-Boeck's Disease and Uveoparotid Fever (Heerfordt), Nederl. tijdschr. v. geneesk. **80**:2859, 1936.

12. Longcope, W. T., and Pierson, J. W.: Boeck's Sarcoid (Sarcoidosis), Bull. Johns Hopkins Hosp. **60**: 223, 1937.

13. Pautrier, L. M.: Les lesions oculaires de la maladie de Besnier-Boeck-Schaumann (le syndrome de Heerfordt), Arch. d'opht. **2**:689, 1938.

14. Heerfordt, C. F.: Ueber eine "Febris uveoparotidea subchronica" an der glandula parotis und der Uvea des Auges lokalisiert und häufig mit Paresen cerebrospinaler Nerven kompliziert, Arch. f. Ophth. **70**:254, 1909.

the publication of Slot's paper, Hamburger and Schaffer [15] had expressed the view that uveoparotid fever and certain forms of the Mikulicz syndrome associated with uveitis represented the same fundamental condition. Since the publication of the papers by Slot, Longcope and Pierson and Pautrier, it is generally recognized that these conditions are both manifestations of sarcoidosis.

While sarcoidosis may affect the ocular adnexa as small nodules in the conjunctiva, lids, episcleral tissues and orbit, such lesions are of little importance except for the diagnostic problem they present. The important ocular lesions are those affecting the uveal tract. Notable among the many reports on the ocular complications of sarcoidosis are those of Pautrier [13] (1938), Walsh [16] (1939) and Levitt [17] (1941). The most characteristic clinical picture is nodular iritis, quite similar to the nodular iritis of tuberculosis, although the nodules have a tendency to be larger, slightly pinker and more vascularized. The iritis is characteristically quite painless. Again, there may be no macroscopically visible nodules but the inflammatory reaction is pronounced. In either type posterior synechia may form, and the picture may develop into generalized uveitis, with blurring of the media, secondary clouding of the lens, keratitic deposits and changes in the posterior portion of the uvea. In some cases the condition may progress to secondary glaucoma and finally to phthisis bulbi, but the general tendency is more favorable. The nodules tend to become hyalinized; the inflammatory symptoms disappear, and the entire process may subside without residua. Involvement of the posterior part of the uvea without change in the anterior portion is comparatively rare, but several cases have been reported, the ophthalmoscopic picture being that of small spots or larger nodular exudates in the choroid, with slight surrounding inflammatory reaction. Primary infiltration of the cornea does not occur, any corneal clouding being secondary to the disease in the anterior part of the uvea.

In almost 500 cases of sarcoid reviewed by Osterberg [18] only 27 instances of uveitis were mentioned specifically, but apparently the eyes were not examined in all cases, the records of

TABLE 3.—*Summary of Data on Fifteen Patients with Uveitis and Histologically Proved Sarcoid*

Age, Yr.	Race	Sex	Ocular Involvement	Keratitic Precipitates	Nodules in Iris	Enlargement of Lymph Nodes	Serum Albumin, Gm. per 100 Cc.	Serum Globulin, Gm. per 100 Cc.	Evidence in Roentgenogram of Chest	Intracutaneous Tuberculin Reaction, Mg. of O. T.*	Evidence in Roentgenograms of Hands and Feet	Fever	Cutaneous Lesions	Peripheral Neuritis	Comment
13	W	M	Bilateral; generalized	Large	—	Generalized	3.3	2.7	+	—10	—	+	+	—	
15	N	F	Bilateral; generalized	Large	Large	None	3.2	5.1	—	+0.01	—	—	—	+ (VII)	
18	N	M	Unilateral; generalized	Large	Large	Few	4.0	3.3	+	+0.01	—	+	—	—	
19	W	M	Bilateral; generalized	Large	—	Few	5.3	2.3	+	—0.001	ND†	—	—	—	
21	N	M	Unilateral; anterior	Small	—	Few	4.4	3.3	+	—0.1	ND	—	—	—	
25	N	F	Bilateral; generalized	Large	—	Few	3.6	4.8	+	—3	—	—	—	—	Keratitis also
26	N	M	Bilateral; generalized	Large	Large	Few	4.6	3.6	+	+1	ND	—	+	—	
29	W	F	Unilateral; generalized	Large	Large	Few	5.0	2.0	+	—10	—	—	—	—	
30	N	M	Bilateral; posterior	—	—	Generalized	3.9	4.4	—	+0.01	—	+	—	—	Retinal periphlebitis also
30	N	M	Bilateral; anterior	Small	—	Generalized	ND	ND	ND	ND	ND	—	—	—	Enlarged lacrimal glands
31	W	F	Bilateral; generalized	Large	Large	Few	ND	ND	—	—1	—	—	—	—	
33	N	F	Bilateral; anterior	Large	—	None	3.0	4.6	+	+1	ND	+	+	+ (X and XII)	
47	W	M	Bilateral; generalized	Large	Large	Few	ND	ND	+	+10	—	—	—	—	
53	W	F	Bilateral; anterior	Large	Large	None	4.6	2.3	+	—0.1	—	—	—	—	
67	W	M	Bilateral; generalized	Large	—	Few	4.4	2.8	+	+0.1	—	—	—	—	Keratitis also

* Tuberculin reactions if positive (+) are listed as the smallest dose to which the patient was sensitive; if negative (—), as the largest dose with which the patient was tested.

† ND indicates that the examination was not determined or made.

15. Hamburger, L. P., and Schaffer, A. J.: Uveoparotid Fever as a Manifestation of Mikulicz's Syndrome, Am. J. Dis. Child. **36**:434 (Sept.) 1928.

16. Walsh, F. B.: Ocular Importance of Sarcoid: Its Relation to Uveoparotid Fever, Arch. Ophth. **21**: 421 (March) 1939.

17. Levitt, J. M.: Boeck's Sarcoid with Ocular Localization: Survey of the Literature and Report of a Case, Arch. Ophth. **26**:358 (Sept.) 1941.

18. Osterberg, G.: Iritis Boeck (Sarkoid of Boeck on Iris), Brit. J. Ophth. **23**:145, 1939.

most of these cases being collected from the dermatologic literature. In contrast, Levitt [17] found that of 100 patients with sarcoidosis whose cases had been reported since 1936, 28 had uveitis and 10 phthisis bulbi. Of 29 patients with proved sarcoidosis studied in the Johns Hopkins Hospital within the past four years, 15, or 52 per cent, had active uveitis. This evidence indicates that ocular involvement is one of the most frequent manifestations of sarcoidosis.

Fig. 2.—Nodules in the iris in a case of sarcoidosis. *A*, early stage, and *B*, late stage.

Previous reports give no indication of the statistical importance of sarcoidosis in patients with uveitis. The incidence of proved sarcoidosis in this series (7.5 per cent) is undoubtedly too high for all forms of uveitis. Only about one third of the general run of patients with uveitis seen at the Wilmer Ophthalmological Institute are admitted for study or treatment. However, during the period covered by this report, practically all patients with uveitis in whom there was any suspicion of sarcoidosis were admitted for clinical study and biopsy. Therefore, the incidence of sarcoidosis among patients with endogenous uveitis as a whole should be about 2 or 3 per cent. The percentage of cases of uveitis associated with sarcoidosis is probably much lower in some sections of this country, because Negroes (common in Baltimore) are much more likely to have sarcoidosis than are white persons.

The 15 patients with sarcoidosis reported in this paper presented no significant sex distribution of the disease, 9 being males and 6 females. There appears, however, to be some predilection of the disease for Negroes, 8 of the patients being Negroes, a ration out of all proportion to the general racial distribution in this region. This is in accord with the incidence in other reports. The ages of our patients ranged from 13 to 67 years. The significant data on the 15 patients are shown in table 3.

The uveitis in the 15 patients with sarcoidosis reported on in this series was bilateral in 12 patients and unilateral in 3 patients. It was always chronic and often severe. The general tendency was for the entire uveal tract to be involved, although the disease was limited to the iris in 3 patients and to the choroid in 1 patient. While the most characteristic symptom of ocular sarcoidosis is nodules in the iris, such lesions were present in only 7 of our patients. The nodules were similar to those described by other authors, being slightly larger, more irregular and somewhat more vascularized than those present in tuberculous iritis (fig. 2). They sometimes disappeared without a trace, in contrast to tuberculous nodules in the iris, which always leave small scars of atrophy where they heal. In the 7 patients with iritis without nodules the picture was clinically indistinguishable from the usual one of chronic granulomatous uveitis. Only 2 of the patients in this series showed deep keratitis and corneal vascularization. Keratitic deposits were observed in all 14 of the patients with anterior involvement. The deposits were usually large, of the mutton fat, epithelioid cell type. In only 2 patients were small lymphocytic deposits observed. In the 1 patient with choroiditis, the lesions were small, poorly outlined and multiple, and there was questionable associated periphlebitis.

The general course of the ocular disease was usually less severe than that of tuberculous uveitis, and several of the eyes healed without any residual damage. However, in several patients involvement of the uveal tract was extreme, and in 1 patient the eye progressed to phthisis bulbi and was enucleated. Histologically, this eye contained a number of moderately large nodules consisting of epithelioid cells and giant

cells (fig. 3). No Schaumann bodies were visible. These nodules were most prominent in the peripheral portions of the iris and in the ciliary body. There were also some diffuse infiltration of lymphocytes in the iris and ciliary body and a few polymorphonuclear leukocytes. The choroid was normal except for small accumulations of lymphocytes. The anterior chamber contained considerable blood, and there were extensive anterior and posterior synechiae. The lens was surrounded by a thin cyclitic membrane.

All 15 of the patients showed systemic manifestations of sarcoidosis. The most frequent lesion was diffuse infiltration of the lungs, this being present in 11 of 14 patients. Glandular enlargement was present in 12 of the patients, but only in 3 was it generalized, being limited in the rest to a few areas, the submental, the cervical, the inguinal or the axillary glands. It is notable that in the 3 patients with no clinical glandular enlargement, biopsy of an apparently normal gland revealed typical lesions of sarcoidosis. Three patients showed only cutaneous lesions, and 2 had peripheral neuritis. Only 4 patients had any fever during the period of observation. In none of the 10 patients who had roentgenograms taken of the hands and feet were any lesions noted in the bones. While it is generally recognized that the distribution of lesions in sarcoidosis is spotty, it is nevertheless interesting that in this group of patients the ocular lesions occurred predominantly in association with pulmonary lesions and glandular enlargement, lesions of the skin and bone being notably few.

Estimations of the albumin and globulin of the serum were made for 13 of the 15 patients; in only 7 patients was the globulin increased more than 3 per cent.

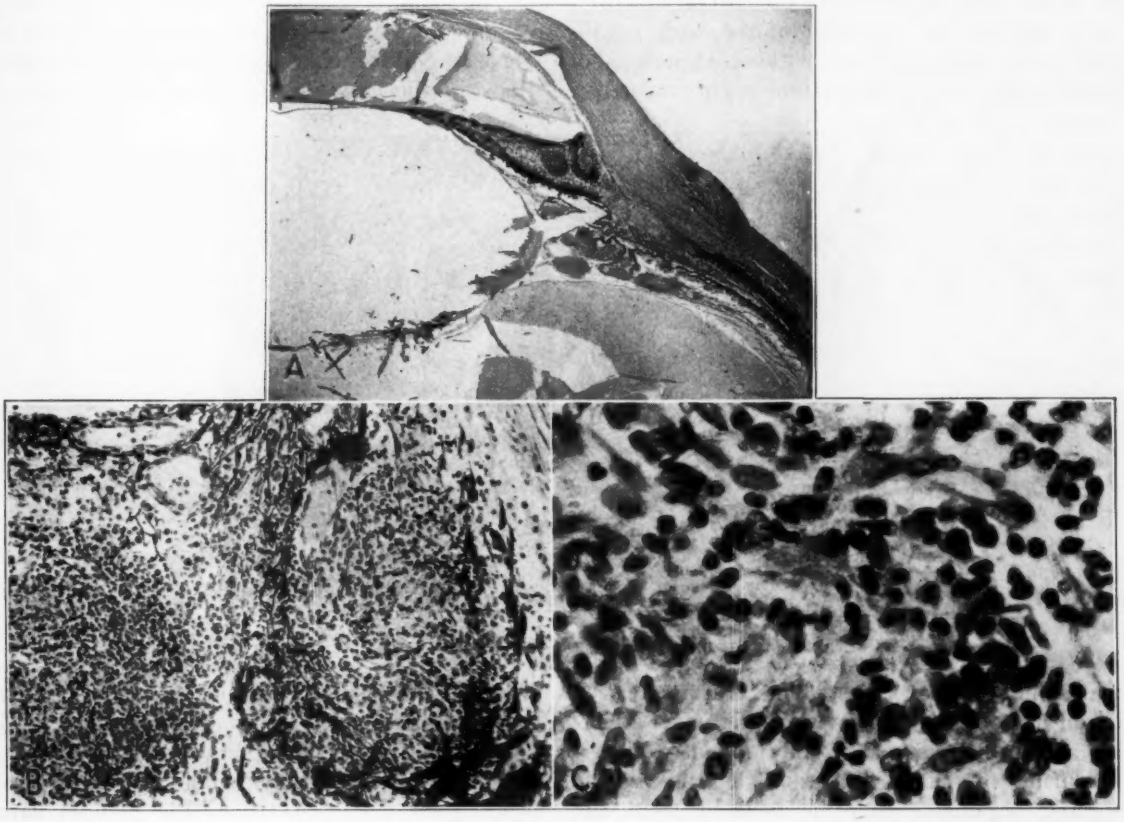

Fig. 3.—Photomicrographs in a case of uveitis accompanying sarcoidosis. *A*, low magnification; *B*, medium magnification, and *C*, high magnification.

Determinations of the sensitivity to tuberculin were made for 14 of these patients. Only 3 patients reacted to 0.01 mg. of old tuberculin, while 5 were completely insensitive to 1 mg. To several of these patients greater amounts of tuberculin were given. Two patients were completely insensitive to the enormous dose of 10 mg., and 1 patient showed only a slight reaction to such a dose.

Brucellosis.—Brucellosis is also known as undulant fever, melitensis, Malta fever and Mediterranean fever. The term brucellosis is derived

from the name of Bruce,[19] who in 1887 isolated the specific organism (Brucella melitensis) from patients with so-called Malta fever. A similar organism (Brucella abortus) was isolated by Bang[20] in 1897 from cows with infectious abortion. In 1913 a third strain (Brucella suis) was isolated from swine.[21] The essential identity of all these organisms was shown by Alice Evans,[22] in 1918, and subsequently the strains of organisms found in animals were shown also to be pathogenic for man.

In man, the disease usually goes through an acute phase, characterized by fever, sweats, malaise, diffuse muscular pains and aches, loss of weight and various more or less vague symptoms affecting any portion of the body. This acute attack may subside without sequelae, but usually the patient passes into a chronic phase, which may last for years. This is characterized by an intermittent low fever, vague pains affecting almost any part of the body and lassitude.

During the acute phase of the disease the specific organisms may be isolated from the blood stream, and a high agglutination titer (up to 1 : 10,000) is shown by the blood serum. As the disease passes into the chronic stage, the organisms can no longer be cultivated; and the agglutination titer drops, sometimes even falling to zero. A positive complement fixation reaction usually develops against the bacterial antigens of B. melitensis, B. abortus or B. suis. The diagnostic validity of this reaction, however, is somewhat vitiated by the fact that Brucella antigens tend to give false positive reactions or cross reactions with antigonococcus serums. As the patient becomes resistant to the disease, a high opsonocytophagic index may develop. Most irregular of all is a cutaneous sensitivity to brucella organisms, which may develop in cases of the chronic form of the disease. There is no leukocytosis, but often lymphocytosis is present.

The general pathologic changes in acute brucellosis are scanty and are probably limited to chronic passive congestion. In chronic infections in the brucellas there is proliferation of cells of the reticuloendothelial system, especially the spleen and lymph nodes, in the form of small nodules (fig. 4). These tiny nodules often resemble tubercles, with epithelioid cells and sometimes giant cells. At times the nodules have necrotic centers, with polymorphonuclear cells in and around the necrotic zone. Such central necrosis is not regularly noted, but when present it aids in differentiating the lesion from tuberculosis. The heart occasionally shows vegetative endocarditis. Nodular reactions in the meninges are common, and occasionally degenerative changes are seen in nerve cells.

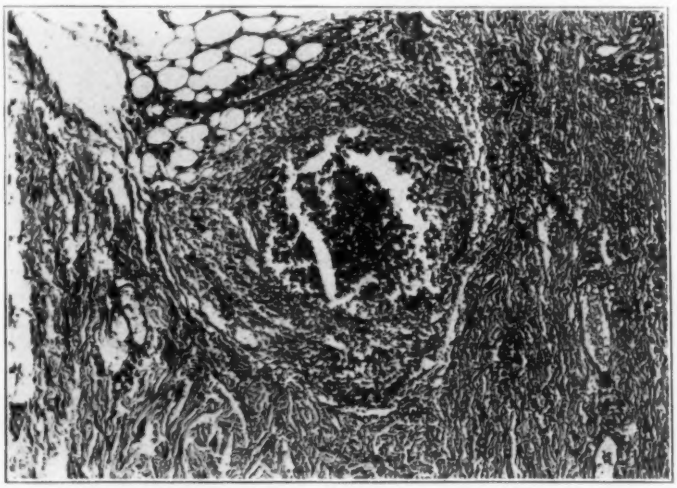

Fig. 4.—Photomicrograph of a lymph node in a case of chronic brucellosis.

The diagnosis of brucellosis presents considerable difficulty. In the acute stage it is suggested by the clinical picture and by a history of exposure or the ingestion of raw milk or its products. In the chronic stage the diagnosis is suggested by an unexplained intermittent fever, vague general symptoms with pain in the muscles

19. Bruce, D.: Notes on the Discovery of a Microorganism in Malta Fever, Practitioner **39**:161, 1887.

20. Bang, B.: Die Aetiologie des seuchenhaften (infectiösen) Verwerfens, Ztschr. f. Thiermed. **1**:241, 1897.

21. Traum, J.: Annual Report of the Chief, United States Department of Agriculture, Bureau of Animal Industry, 1914, p. 30.

22. Evans, A. C.: Further Studies on Bacterium Abortus and Related Bacteria: II. A Comparison of Bacterium Abortus with Bacterium Bronchiseptus and with the Organism Which Causes Malta Fever, J. Infect. Dis. **22**:441, 1912.

and joints, lassitude and a history of a former, more acute, phase and of the ingestion of raw milk or its products. The only laboratory tests of any value are the serologic and sensitivity reactions. Since in the chronic stage the agglutination titer is usually low, and may even be absent, considerable significance should be attached to weak positive reactions. By use of living organisms in the antigen, weak agglutination reactions may be detected which might be missed with a less sensitive antigen. Positive reactions in complement fixation tests must be controlled by similar tests against gonococcus antigens. A low opsonocytophagic index has no diagnostic significance, and a high index means only that the patient has some resistance against the organisms. All these tests, together

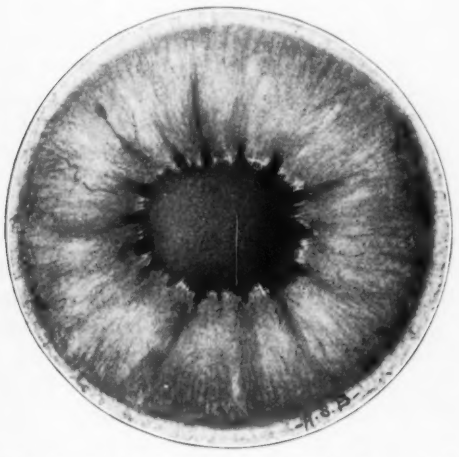

Fig. 5.—Iritis in a case of chronic brucellosis.

with demonstrable cutaneous sensitivity against brucella organisms, only indicate that the patient has had the disease. They do not indicate with certainty that the disease is still active, since a positive reaction may be the residuum of an acute infection from which recovery has been made.

The evidence that systemic infection with the brucella can cause endogenous ocular disease is based on experimental and clinical observations. In 1912 Fabyan [23] reported 3 cases of deep keratitis in infected guinea pigs, lymphocytic infiltration and tubercles in the cornea being observed histologically. Organisms were recovered from the eyes of these animals. In 1928 Orloff,[24] in a comprehensive study of the experimental ocular lesions in guinea pigs, reported that endogenous ocular disease occurred in about 10 per cent of inoculated animals. The affected eyes showed pericorneal congestion; multiple round corneal infiltrates, either central or peripheral, and definite iritis, with exudates over the pupillary space. Histologically, these eyes showed diffuse and focal infiltration of the iris and ciliary body with lymphocytes and epithelioid cells and only minor changes in the choroid. Direct inoculation of organisms in the eyes of rabbits (Burky,[25] 1939) produced generalized keratouveitis almost indistinguishable clinically from severe tuberculous lesions. Interest in ocular brucellosis was stimulated by the presentation of bacteriologic and serologic evidence that most horses with periodic ophthalmia (recurrent endogenous uveitis) are infected with brucellas.

The first clinical observation on ocular brucellosis was reported in 1924 by Lemaire,[26] who studied a case of bilateral optic neuritis in a patient with acute brucellosis, from whose spinal fluid the organisms were isolated. Thereafter, a sprinkling of cases of various types were reported. In 1939 McGinty and Gambrill [27] listed iritis as a recognized complication of brucellosis. In the same year the reported cases were collected by Green,[28] who added 4 of his own. In Green's series were 7 cases of nonrecurrent uveitis in patients with acute brucellosis. The relative infrequency with which uveitis is associated in the acute human brucellosis is indicated by this small number found among hundreds of reported cases of proved brucellosis. Also, Rutherford,[29] in ophthalmoscopic examination of 63 patients with brucellosis, observed changes in the disks in 3, but no uveitis.

The ocular picture in the 15 patients in this series in whom the uveal inflammation was attributed to brucella infection was in no way characteristic or memorable. In 7 of the patients the picture was that of simple recurrent iritis. In 1 patient there were definite nodules in the iris; in another, questionable deep nodules (fig. 5) and in a third, Koeppe nodules. In 3 patients the changes were limited to the choroid, the usual picture being one or more elevated, moderately circumscribed, areas of exudate with little surrounding reaction or generalized subretinal

23. Fabyan, M.: A Contribution to the Pathogenesis of Br. Abortus Bang, J. M. Research **26**:441, 1912.

24. Orloff, K. C.: Melitokokkia (Malta Fieber) und Auge, Klin. Monatsbl. f. Augenh. **81**:582, 1928.

25. Burky, E. L.; Thompson, R. R., and Zepp, H. M.: Role of Brucella in Ocular Disease with Special Reference to Periodic Ophthalmia in Horses, Am. J. Ophth. **22**:1210, 1939.

26. Lemaire, M. G.: Meningite a melitocoques: Alterations importantes du liquide cephalo-rachidien hyperglycorachie; guerison, Bull. et mém. Soc. méd. d. hôp. de Paris **48**:1636, 1924.

27. McGinty, A. P., and Gambrill, W. E.: Chronic Brucellosis, Internat. Clin. **1**:1, 1939.

28. Green, J.: Ocular Manifestations in Brucellosis (Undulant Fever), Arch. Ophth. **21**:51 (Jan.) 1939.

29. Rutherford, C. W.: Papilledema in Undulant Fever, J. A. M. A. **104**:1490 (April 27) 1935.

edema (fig. 6). In 1 patient there was associated papilledema. In 5 patients the picture was that of generalized uveitis, progressing in 1 to phthisis bulbi. In 12 patients the uveitis was bilateral and in 3 unilateral. In 11 of the 15 patients the uveitis was recurrent. In 8 patients the uveitis appeared to be of the granulomatous type, with thickening of the iris, posterior synechiae and heavy deposits of epithelioid cells on Descemet's membrane. In 7 patients the uveal inflammation was of the nongranulomatous type, without nodular changes in the iris and with only small keratitic deposits of lymphocytes.

In 2 patients there were associated changes in the cornea. In 1 patient these were limited to slight peripheral vascularization, while in the second the picture was that of nummular keratitis. We have also seen typical nummular keratitis in another patient with chronic brucellosis. The keratitis was not associated with uveitis and the patient was not included in the present series. These 2 cases, however, suggest the question whether there is any etiologic relation between brucella infection and nummular keratitis. One of the commonest ocular signs associated with experimental brucellosis are corneal infiltrates, similar to those present with nummular keratitis. Further study of cases of nummular keratitis for the possibility of brucella infection is needed for elucidation of this question.

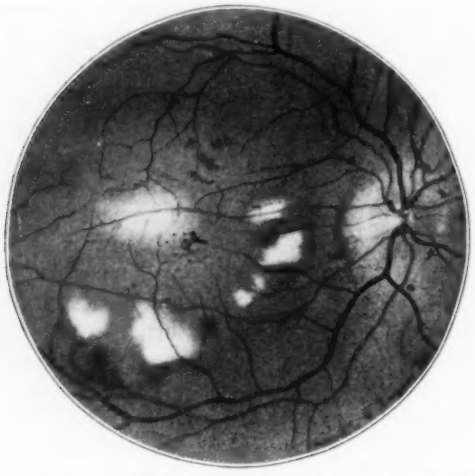

Fig. 6.—Choroiditis in a case of chronic brucellosis.

In 1 patient in this series the uveitis had progressed to phthisis bulbi. The eye was painful and was enucleated. Histologic examination showed nonspecific uveitis with several conspicuous lymphoid nodules (fig. 7), a picture suggestive of that of periodic ophthalmia in horses.

None of these patients exhibited any symptoms of acute brucella infection, and only 1 patient had a prolonged, low grade fever. Most of the patients had a history of a previous unexplained fever, with malaise and various vague symptoms. On careful questioning every patient gave the history of ingestion of raw milk or raw milk products, and several had had contact with animals with probable brucella infection. Some of the patients were below par from a general physical standpoint; but others were reasonably healthy, and a few were actually robust.

The clinical diagnosis of brucellosis for these patients was of necessity based almost entirely on serologic and sensitivity reactions as evidence of the infection, although it was bolstered by a suggestive history. Brucellas were not cultured in any case, and, unlike the cases reported by Greene, the disease of all these patients must be considered to be in the chronic, or possibly the healed, stage. Agglutination tests, done against antigens of living B. suis and B. abortus organisms, gave positive reactions in dilutions of 1:40 to 1:320 in 12 of the 15 patients. One patient had an agglutination titer of only 1:20. In another patient the agglutination reaction was negative, but the complement fixation reaction was strongly positive. In the last patient both the agglutination and the complement fixation test gave negative reactions, but the test for cutaneous sensitivity was violently positive, and no other etiologic factors were found. Tests for cutaneous sensitivity were not done routinely, for the reason that they appeared to disturb and to invalidate later agglutination tests. They were made on 5 patients, with a positive reaction in 4 patients and a negative reaction in 1 patient. Complement fixation tests for brucellosis were performed on 8 of these patients, with positive reactions in 6 patients.

Positive serologic or sensitivity reactions are, in the last analysis, only evidences that the patient has at one time in life had a brucella infection, from which he may have recovered, or the disease may have passed into the chronic stage. Moreover, brucellosis is a relatively widespread disease. The question, therefore, arises: What significance should be attached to these positive reactions?

In the entire series, agglutinations against the brucella antigen were performed on 176 patients and gave positive reactions for 22, an incidence of 13 per cent. If the positive reactions are of diagnostic significance, and if brucellosis is an important factor in the causation of uveitis, the percentage incidence of positive agglutination reactions should be higher in a series of patients with uveitis than in a series of "normal" patients,

and should be somewhat comparable to the percentage incidences in medical patients in whom brucellosis was suspected as a factor responsible for their various symptoms. Unfortunately, we have no control series of normal subjects for comparison of positive reactions, but we have a series of 47 medical patients in whom for various reasons chronic brucellosis was suspected and statistical proof, that the incidence of brucellosis was higher than normal in the series of patients with uveitis. Of the 22 patients with uveitis with positive agglutinations to brucella, only 8 (36 per cent) had definite evidence of some other factor which appeared to be a cause of the uveitis. Thus, while the incidence of other factors is slightly lower in patients with positive agglutination re-

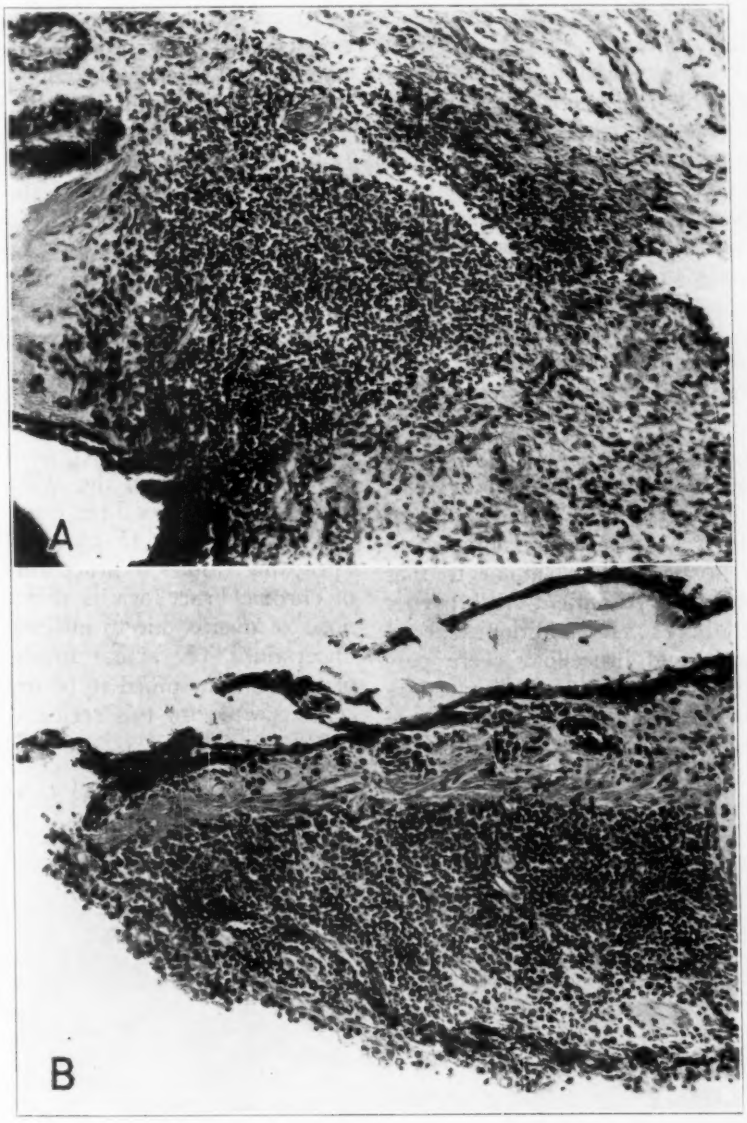

Fig. 7.—Photomicrographs in a case of uveitis associated with brucellosis. *A*, lymphoid nodule at the root of the iris; *B*, lymphoid nodule near the sphincter of the iris.

whose serums were sent to the Wilmer Institute for examination. Eight of these patients gave positive reactions, an incidence of 17 per cent. Thus, the incidence of positive agglutination reactions in the entire series of patients with uveitis was almost as high as that in a group of medical patients suspected of having chronic brucellosis. This evidence suggests, but is not actions to Brucella, the difference is not of statistical significance. It is impossible, therefore, from the evidence now available to obtain statistical proof that a positive agglutination reaction to Brucella is of diagnostic significance in establishing the cause of uveitis. Such a positive reaction is, however, suggestive evidence, and in general is probably of about the same value in the diagnosis

of uveitis due to brucellosis as is moderate hypersensitivity to tuberculin in the diagnosis of tuberculous uveitis.

A total of 76 complement fixation reactions for both the brucella and the gonococcus were performed on patients in this series. Twenty-one patients gave a positive reaction to the brucella, but 18 of these also showed a positive reaction to the gonococcus.

It is clear the diagnosis of chronic brucellosis as the etiologic factor in uveitis must always be presumptive, since the isolation of the actual organism is impossible and there is no therapy so adequate that it can be applied as a therapeutic test. However, despite the presumptive character of the diagnosis, the accumulated evidence indicates that brucellosis is probably an etiologic factor in uveitis, and it may be an important one.

Since a diagnosis of chronic uveitis due to Brucella can never be made with certainty, the incidence shown in this study (7.5 per cent) represents a maximum. The actual incidence of this form of uveitis may be anywhere below this figure.

SUMMARY

A series of 200 patients with endogenous uveitis examined in the Wilmer Institute between July 1, 1939 and July 1, 1943 was subjected to an extensive diagnostic survey, similar to that carried out in a series of 562 patients with uveitis previously reported on. In addition, special tests for sarcoidosis and brucellosis were performed on this series of patients. Such tests were done routinely whenever either of these diseases was suspected. Biopsies of the lymph nodes for diagnosis of sarcoidosis were performed on 51 patients, and determinations of the levels of albumin and globulin in the blood were made on 71 patients. Agglutination tests for Brucella were carried out on 176 patients; complement fixation tests for Brucella, on 76 patients, and determinations of the opsonocytophagic index of the organism, on a number of patients.

In the etiologic classification, a diagnosis of uveitis due to sarcoidosis was made for 15 patients. A histologic diagnosis of sarcoidosis was made for each of these patients. In this group of patients it was noted that the lesions of the skin and bone were notably scarce, that normal levels of globulin in the serum were encountered much more frequently than has been reported for other series of patients with sarcoidosis and that biopsy of a lymph node may yield evidence of this disease even though the lymph gland is not enlarged. Since strictly outpatients were excluded from this series, it is assumed that the uveitis was much more severe than in the usual series of cases and that the actual incidence of sarcoidosis in patients with uveitis examined in the Wilmer Institute is in the neighborhood of 3 per cent.

The uveitis of 15 patients was classified as "probably" due to brucellosis. The diagnosis of chronic brucellosis is difficult, and any diagnosis of uveitis due to infection with Brucella is uncertain. The actual incidence of this form of uveitis is assumed to be less than the 7.5 per cent reported for this series.

Wilmer Ophthalmological Institute.

DEVELOPMENT OF ANTERIOR PERIPHERAL SYNECHIAE IN EXPERIMENTAL ACUTE GLAUCOMA

MANUEL URIBE TRONCOSO, M.D.

NEW YORK

To the memory of my friend, the distinguished ophthalmologist, Dr. John Martin Wheeler.

It has long been debated whether the cause of hypertension associated with acute or subacute congestive glaucoma is exclusively a mechanical one, produced by the application of the root of the iris against the corneal limbus, or whether, on the contrary, the anterior peripheral synechia is the result of preexisting hypertension. Historically, the first position was substantiated by Knies and Weber,[1] who in glaucomatous eyes examined with the microscope always observed an adhesion of the root of the iris to the cornea. However, several observers, including myself,[2] objected that the microscopic sections were made in old glaucomatous eyes enucleated after the process had run its course. On the other hand, microscopic examination of eyes with acute or subacute glaucoma which were removed shortly after the attack, when the patient died of an intercurrent disease (Birnbacher and Czermak [3] and Elschnig [4]), showed that the anterior chamber was totally or partially free from synechiae.

With the advent of gonioscopy the examination of the angle of the anterior chamber could be made directly in living eyes, and I [5] determined for the first time that in cases of prodromal glaucoma or after an acute attack has subsided the angle of the anterior chamber is usually open, either totally or partially. Other authors have confirmed these observations (Werner [6] and Sugar [7]).

Recently, however, the theory of mechanical occlusion of the angle by peripheral synechiae as the principal cause of acute glaucoma has been revived by Sugar [7] and by Kronfeld and Grossman.[8] They based their opinion on the occurrence of the so-called mydriatic glaucoma, which starts immediately or soon after the use of homatropine. Sugar, by gonioscopic examination of such eyes before and after the attack, was able to observe that during hypertension the dilated iris blocked the angle of the anterior chamber. This occurred especially in patients who had shallow chambers, and the root of the iris was near the corneal limbus. By photographic methods, Sugar measured the depth of the anterior chamber in 20 eyes with narrow angles before mydriasis and then instilled homatropine. In 6 of these eyes an attack of acute glaucoma occurred. Sugar and Kronfeld and Grossman concluded that the pathogenesis of the acute attacks is determined, first, by a shallowness of the anterior chamber and, second, by the application of the root of the iris against the trabeculum, which blocks the outflow through the Schlemm canal and upsets the balance of the intraocular pressure. If the upset lasts for several days, the mere contact of the iris to the limbus is transformed into a permanent synechia. Although, of course, in these 6 eyes a mechanical occlusion of the angle may have been the prime factor which started the cycle of hypertension, I do not think this etiologic explanation ought to be extended to include all cases of glaucoma. One should remember that in the other 14 eyes, the majority of which were the fellow, normal eyes of patients with unilateral glaucoma, the mydriatic did not produce any hypertension, al-

This study was aided by a grant from the Harriman Glaucoma Fund.

From the Department of Ophthalmology, Columbia University, and the Ophthalmological Institute of the Presbyterian Hospital.

1. Knies, M.: Ueber das Glaucom, Arch. f. Ophth. (pt. 3) **22**:163, 1876; (pt. 2) **23**:62, 1877. Weber: Die Ursachen des Glaukoms, ibid. (pt. 1) **23**:1, 1877.

2. Uribe Troncoso, M.: Pathogenie du glaucome: Recherches cliniques et experimentales, Ann. d'ocul. **126**:401 (Dec.) 1901; An. de oftal. **4**:97 (Oct.) 1901.

3. Birnbacher, A.: Beitrag zur Anatomie des Glaucoma acutum, Graz, Leuschner & Lubensky, 1890. Birnbacher, A., and Czermak, W.: Beiträge zur pathologischen Anatomie des Glaucoms, Arch. f. Ophth. (pt. 2) **32**:1, 1886; (pt. 4) **32**:1, 1886.

4. Elschnig, A.: Anatomische Untersuchungen zweier Fälle von acutem Glaucom, Arch. f. Augenh. (supp.) **33**:187, 1896.

5. Uribe Troncoso, M.: Gonioscopy and Its Clinical Applications, Am. J. Ophth. **8**:433, 1925.

6. Werner, S.: Gonioskopische Untersuchungen bei Glaucoma primarium, Acta ophth. **10**:427, 1932.

7. Sugar, H. S.: The Mechanical Factors in the Etiology of Acute Glaucoma, Am. J. Ophth. **24**:851, 1941.

8. Kronfeld, P. C., and Grossman, E. E.: The Relation of Gonioscopic Findings to the Incidence of Secondary Glaucoma in Operative Aphakia, Tr. Am. Acad. Ophth. (1940) **45**:184, 1941.

though the dilation of the pupil undoubtedly narrowed the entrance to the chamber recess.

As it is difficult to examine the angle of the anterior chamber with the gonioscope during the acute attack on account of the edema and turbidity of the cornea, I have tried to determine experimentally whether the adhesion of the root of the iris is the first step in the production of glaucoma. Unfortunately, there is at present no method of reproducing primary glaucoma experimentally in animals. There have been many attempts to do so by injection of different substances into the anterior chamber or into the vitreous with observations on the variations in tension, the changes produced in the angle of the anterior chamber and the condition of the optic nerve. Injections in the anterior chamber were made, first, with organic substances, such as olive oil (Wever), vitreous (Bajardi), lipids (Weintraub), albumin and serum (Uribe Troncoso) and paraffin emulsion (Ishikawa), and, second, with inorganic substances, such as electrolytic iron (Erdmann, Schreiber and Wengler), dyes (Hamburger) and scarlatoid (Seidel).

Hypertension of a temporary course has been produced by mechanical lesions in the angle (Bentzen), by contusion of the globe (Pesme, Leplat), by cauterization of the limbus with acids (Heirsrath), by irritation of the iris (Magitot) and by discission of the lens (Wessely). Injections in the vitreous have been undertaken with isotonic solution of sodium chloride, by S. Larson; with a solution of sodium oxide, by Redslob, and with histamine, by Duke-Elder and Friedenwald. Ligature of the veins of the vortex (Schulten, Leber, Magitot) produced great venous stasis, with extreme hypertension of a temporary nature.

Unfortunately, the procedures of injection of foreign substances are crude and the results distorted by traumatic and inflammatory conditions. After considering all these methods, I concluded that from the physiologic and pathologic standpoints the best procedure is to use the animal's own serum or blood and to inject it into the anterior chamber or the vitreous. In clinics the production of hypertension, and even permanent glaucoma, is observed after abundant hemorrhages in the anterior chamber. After injuries, and more frequently after operations such as iridectomy and cataract extractions, an increase in tension develops, sometimes of considerable degree, and may last for weeks or months. It may disappear entirely or leave permanent glaucomatous changes.

The following case illustrates this occurrence.

H. M., an obese woman aged 70, with arthritis, gallbladder disease and systemic hypertension, was admitted to the Ophthalmological Institute for operation for senile cataracts. The tension was 25 mm. in each eye. A preliminary iridectomy was done on the left eye on February 25, and atropine was instilled. There was bleeding from the conjunctiva. The blood entered the anterior chamber, filling it almost completely. After the operation the eye remained tender, and three days later it became painful. The tension rose to 52 mm. Physostigmine did not lower the pressure at first, but on the sixth day the tension fell to 35 and 40 mm., with gradual absorption of the clot in the anterior chamber. Paracentesis of the eye was considered but was not done. On March 6 the hemorrhage in the anterior chamber had partially absorbed. The upper half of the cornea was clear, and the tension was reduced to 35 mm. There was still a great deal of pain and congestion. The tension in the right eye also rose temporarily to 29 mm., but there were no definite symptoms of chronic glaucoma.

On May 22 tension had returned to normal in the left eye. The hypemia was then entirely absorbed, but the anterior chamber remained shallow.

Gonioscopic studies at this time showed that the angle was open on all sides. It was not considered probable that if a peripheral synechia existed at the beginning of hypertension, no traces of it would be evident in this examination.

Intracapsular extraction was performed on this eye by Dr. D. Kirby, on June 9, with complete success. No vitreous was lost. With the proper correction, visual acuity reached 20/40. One year later the patient returned for observation. The results of the operation were still good. Gonioscopic examination at this time showed that the angle had closed on the nasal side but remained open in all other parts of the limbus. This closure was considered the late result of the cicatrization of the incision in the limbus.

Experiments with injections of blood into the anterior chamber had been made previously by several investigators. Riehm [9] observed the effects of these injections in normal rabbit eyes in order to compare them with the changes produced in human eyes affected with tuberculous uveitis; he injected pure blood of the patient into the anterior chamber of 16 rabbits, according to the method of Schieck. In 11 of the animals he obtained hypertension of such high degree that the cornea became opaque and spontaneous rupture of the eyeball occurred in the course of the first two days after the injection. In the other 5 rabbits the hypertension was of less degree, and the absorption of blood took place between one and four weeks after operation. In a second series, of 4 rabbits, he injected defibrinated blood. The effects were milder, and no ruptures of the eyeball were produced. The duration of the reaction was about the same as that in the previous series. Riehm observed, also, that the effect of defibrinated blood became weaker the longer the blood stood after defibrination.

9. Riehm, W.: Experimentellen zur lokalen Wirkung körper- bzw. arteigenen Blutes in der Vorderkammer des Kaninchens, Ber. ü. d. Versamml. d. deutsch. ophth. Gesellsch. **49**:188, 1932.

As these experiments were made from the bacteriologic standpoint, no curves of hypertension were recorded. No microscopic sections were made of the eyes operated on. Riehm ascribed the hypertension produced to an inflammatory reaction, due to "hematogenous uveitis." According to him, the coagulated blood is particularly rich in certain histamine-like substances (adenyl acid or adenosine), which possess a stimulating effect. They are produced by the decomposition of the blood platelets. Freund called them "early" and "late" poisons. The blood is absorbed later by lytic and coagulating injection of defibrinated blood. When the autonomic nerve supply is previously severed, no effect on the vasomotor system occurs.

When I began to study the development of anterior peripheral synechiae and tried to determine experimentally whether the mechanical application of the root of the iris is the first step in the production of hypertension, I considered the several methods of inducing an increase of tension and decided that the best was the injection into the anterior chamber or the vitreous of substances present in the body itself, such as blood serum and pure and defibrinated blood.

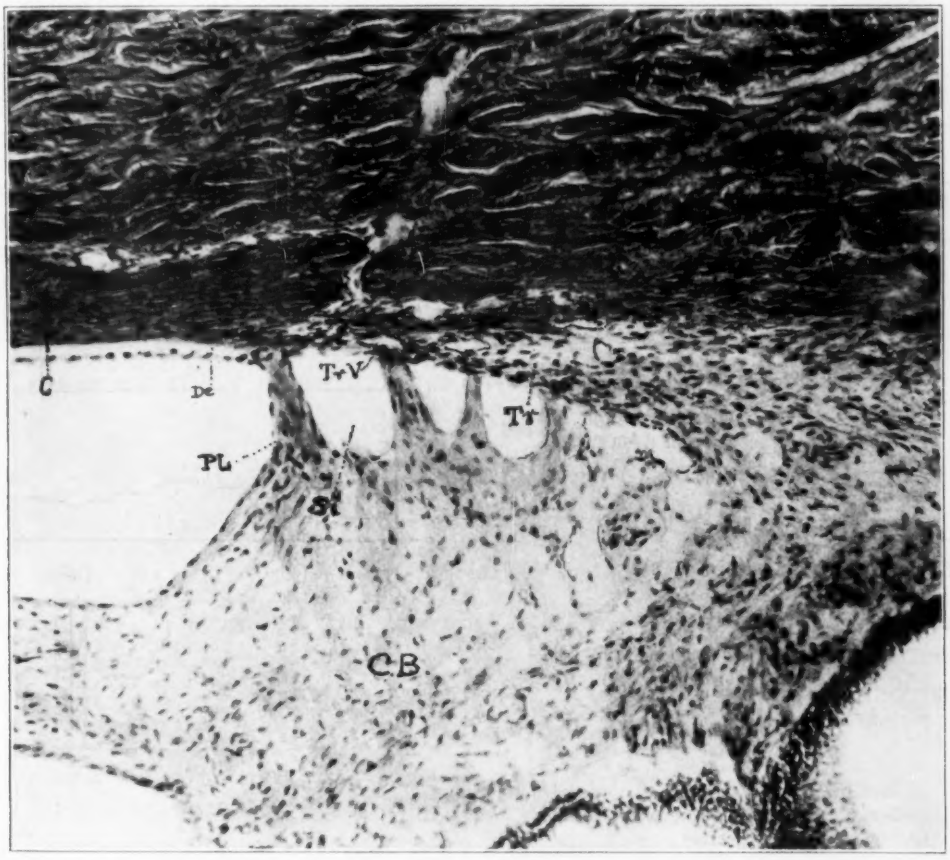

Fig. 1.—Meridional section of a normal rabbit eye (× 45). In this figure, and in the accompanying figures, the following designations are used: *C*, cornea; *D* or *De*, Descemet's membrane; *I*, iris; *PL*, pectinate ligament; *Sc*, sclera; *Si*, ciliosclerał sinus; *Tr*, trabecula; *TV*, trabecular vein, and *CB*, ciliary body.

substances. The general effect of intravenous injection of defibrinated blood has been studied by several authors (Schurer-Waldheim; Hoff; F. Kylin, and Mettenleiter [10]). It immediately produced dilation of blood vessels, combined with reactions of the respective tissues all over the body. These reactions depend on sympathetic and parasympathetic stimulation initiated by the

10. Mettenleiter, M. W.: Autohemotransfusion in Preventing Postoperative Lung Complications, Am. J. Surg. **32**:321, 1936.

The researches described in this paper were conducted only from the physiopathologic standpoint. No effort was made to study changes in the blood in the anterior chamber from the chemical or the bacteriologic point of view.

ANATOMIC CONDITION OF THE ANGLE IN EXPERIMENTAL ANIMALS

The results of animal experimentation cannot be interpreted properly if the observer lacks complete knowledge of the anatomy of the angle

of the anterior chamber and the iris. This omission has led to many errors and encouraged several attempts to consider anatomic and pathologic changes in lower animals as similar to those observed in primates and man. Although the anatomic relations have already been published in other places,[4] a few comments are necessary here for the better understanding of the comparative anatomy of the channels of outflow in the angle of the anterior chamber of rabbits, dogs and monkeys.

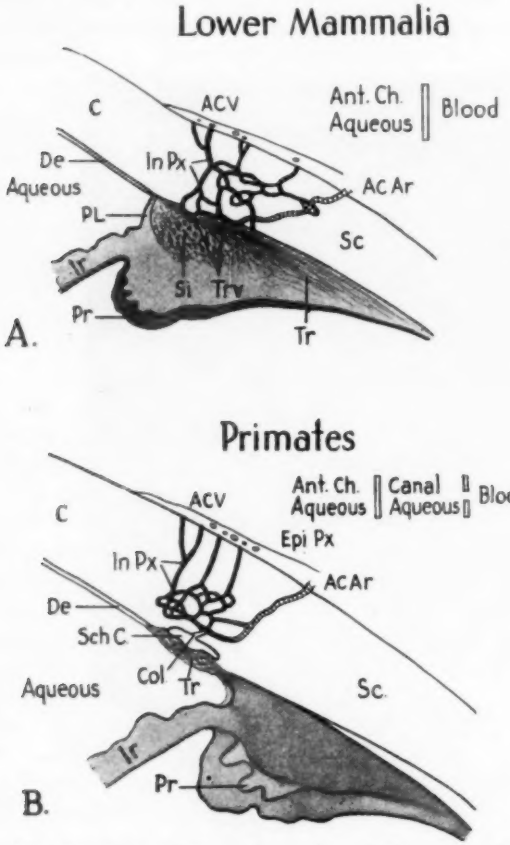

Fig. 2.—*A*, semischematic section of the angle of the anterior chamber in ungulates. Here, and in *B*, *Ir* indicates the iris; *De*, Descemet's membrane; *Si*, cilioscleral sinus, filled with spongy tissue; *In Px*, intrascleral plexus; *Ac Ar*, anterior ciliary artery, and *ACV*, anterior ciliary vein.

B, angle of the anterior chamber in primates. In addition to the designations used in *A*, *Sch c* indicates the canal of Schlemm; *Col*, collector vessel, joined the canal of Schlemm with the intrascleral vascular plexus, and *In Px* and *Epi Px*, the intrascleral and the episcleral plexus.

In the rabbit (fig. 1) the anterior chamber terminates at the end of Descemet's membrane, exactly at the insertion of the teeth of the pectinate ligament into the sclera. Between these teeth the so-called Fontana spaces communicate posteriorly with a recess of the anterior chamber between the ciliary body and the sclera, which I have called the "cilioscleral sinus." In ungulata the sinus is filled with a meshwork of thin, highly pigmented fibers, resembling a sponge (spongy tissue (fig. 2 *A*, *Si*), while in the carnivora (fig. 6 *P*), instead of this tissue, there are a great number of white, fine meridional strands spread fanlike between the end of Descemet's membrane and the inner, and lower, side of the ciliary body.

Running meridionally at the external wall of the sinus there is in mammals a triangular meshwork structure, with its apex at the end of Descemet's membrane (fig. 2 *A*, *Tr*) which is similar in structure to the trabecula occurring in front of the canal of Schlemm in primates (fig. 2 *B*, *Tr*).

The aqueous coming into the cilioscleral sinus through the teeth of the pectinate ligament stays there in contact with a rich network of vessels, which are part of the anterior ciliary system. These intrascleral vessels (fig. 2 *A*, *In Px*) form a dense plexus, many of the superficial branches of which run at the outer side of the trabecula (*TrV*), their inner wall being in contact with the aqueous through the meshes of the trabecula (trabecular veins). These vessels have been

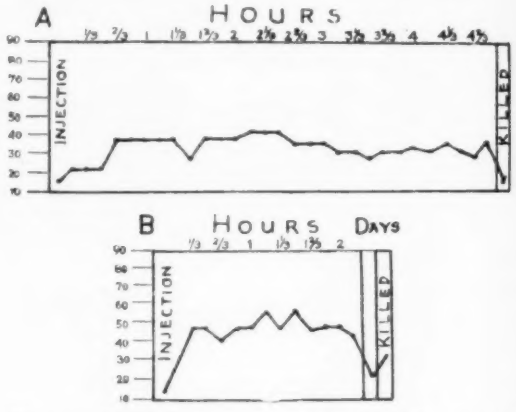

Fig. 3.—Tonometric curves for rabbit 49. *A*, right eye, and *B*, left eye.

compared by former authors to the canal of Schlemm; but, as I have shown elsewhere, there is no canal of Schlemm in lower mammals, and the whole cilioscleral sinus should be considered equivalent from the physiologic standpoint to the canal of Schlemm. At the inner wall of the sinus there are in the ciliary body some vessels, but they do not come superficially in contact with the aqueous. Besides, the hydrostatic pressure of the blood inside them is probably much higher, and they take little part in the outflow of the aqueous.

In monkeys and in man a new organ appears: the canal of Schlemm (fig. 2 *B*), which always occupies the same anatomic place between the

end of Descemet's membrane, high at the upper limit of the trabecula, and the insertion of the ciliary body into the spur. The aqueous is in contact only with the inner wall of the canal of Schlemm, and not with any other vessel of the intrascleral plexus, which runs deep inside the sclera (fig. 2, *In Px*). The canal of Schlemm communicates with the venous plexus only by a few narrow branches, which are called "collectors." The blood does not usually penetrate into the lumen of the canal of Schlemm, as is shown in the normal human eye by gonioscopic inspection.

away, at the inner surface of the cornea, in order to produce a corneal tunnel. This will close the anterior chamber by pressure from within after the injection is made. The aqueous humor is first withdrawn with a sterile syringe; then, with the needle left in place, another syringe is filled with blood and connected with the needle. The injection is made slowly until an amount about the same as that of the aqueous withdrawn is introduced into the chamber. For this maneuver a two way cock attachment is also advantageous. The needle inside the cornea should not be moved in any way, as this widens the puncture and facilitates the leaking of the blood. When the blood flows out from the anterior chamber, incalculable differences may arise in the amount of hypertension.

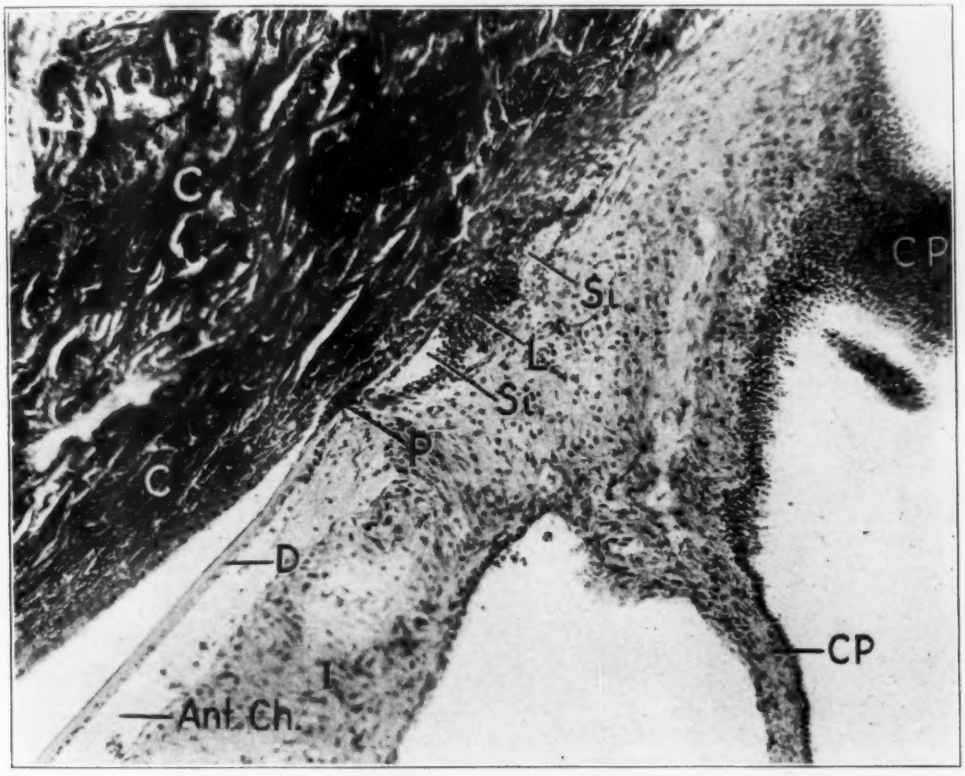

Fig. 4 (rabbit 49; right eye).—Response to the injection of blood serum. *D*, Descemet's membrane, separated from the cornea by an artefact; *Ant Ch*, anterior chamber; *L*, clump of leukocytes inside the sinus, and *CP*, ciliary processes.

TECHNIC OF INJECTION OF SERUM AND BLOOD INTO THE ANTERIOR CHAMBER

The animals were anesthetized either by the method of intraperitoneal injection of pernoston sodium or by ether inhalation. They were also tied securely to special supports for rabbits, dogs or monkeys. In addition, I used a retrobulbar injection of 2 per cent procaine hydrochloride, which is useful in obtaining complete anesthesia of the globe.

To make a perfect injection into the anterior chamber and to avoid the outflow of the injected liquid when the needle is withdrawn, it is necessary to follow a special technic. A needle, 25 gage, is pushed obliquely from the limbus of the cornea into the thickness of the corneal lamella, and a counterpuncture is made far

EXPERIMENTS WITH BLOOD SERUM

Blood taken from the rabbit's heart was centrifuged and the serum, in a sterile condition, injected into the anterior chamber, which had been previously emptied. Two rabbits and 1 dog were employed. Tonometric readings were taken every ten minutes after the injection. Usually the eye became congested, and there was slight chemosis around the limbus. The pupil became smaller. The intraocular tension began to increase about twenty-five minutes after the operation. In rabbit 48 it increased to a considerable height, reaching 65 mm. at the

end of one and three-quarters hours. In rabbit 49, in which operation was performed on both eyes, the tension increased in the right eye to 43 mm. and stayed at about 30 mm. for three and one-half hours after the operation (fig. 3 *A*). In the left eye it reached 55 mm. and next day returned to normal (fig. 3 *B*).

Rabbit 49.—*Pathologic Study.*—Right Eye: The eye was enucleated twenty-eight hours after injection (fig. 4). The angle was filled with serum. There was some reaction, involving especially lymphocytes, polymorphonuclears and neutrophils. The leukocytes were accumulated in the cilioscleral sinus, *Si*. The anterior chamber on the dependent side contained serum, fibrin and scattered leukocytes. The iris, *I*, was somewhat thickened and had a considerable number of dilated vessels. The ciliary processes, *CP*, were normal.

Left Eye: Examination was made two days after injection (fig. 5). The cornea, *C*, was slightly ectatic. There was still a layer of serum and fibrin, *Ser*, in the anterior chamber and on the surface of the iris, *I*. The angle of the anterior chamber was normal in the upper part of the eye, but in the dependent part the iris was close to the cornea and was attached to it by a fibrous layer of proliferating endothelium, *P end* (beginning peripheral synechia). The cilioscleral sinus, *Si*, was filled with serum and migrating leukocytes. The iris, *I*, was thicker; its blood vessels were dilated, and it was covered on the anterior surface by a layer of fibrin. The processes, *PC*, were normal.

Dog 1.—Serum was injected into the anterior chamber of both eyes. Microscopic examination revealed changes similar to those in the rabbit.

Pathologic Changes.—Left Eye (fig. 6): Blood and serum filled the sinus, *Si*, and the spaces between the fanlike fibers of the pectinate ligament, *P*. The iris, *I*, was thicker than normal. The vessels were dilated, and there was considerable edema in the interstices of the stroma. In some of these interstices there were also blood cells, which were similar to those in the anterior chamber, their presence indicating some absorption of the injected fluid by the iris.

Right Eye: The lesions in the iris were similar to those in the other eye, and the edema of the stroma was considerable. Many pigmented globules were scattered between the fibers of the pectinate ligament. The ciliary processes were normal.

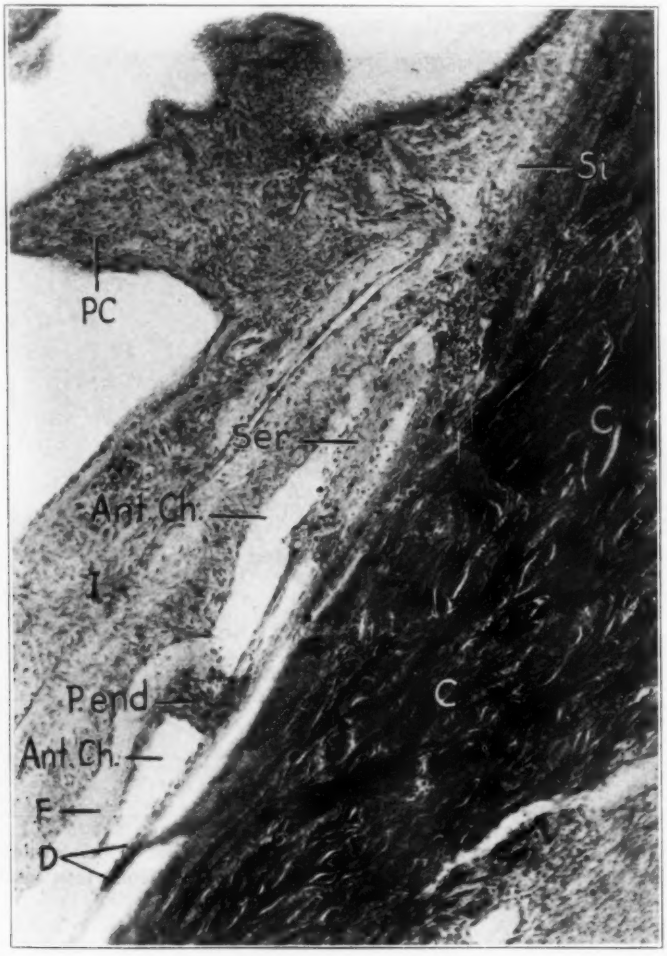

Fig. 5 (rabbit 49; left eye).—Response to injection of blood serum. *Ser*, layer of serum and fibrin in the anterior chamber and on the surface of the iris, *I*; *P end*, end of proliferating endothelium, binding the iris to the cornea, and *F*, layer of fibrin.

EXPERIMENTS WITH DEFIBRINATED BLOOD

Blood was taken directly from the heart of the rabbit, defibrinated and immediately injected into the anterior chamber. The aqueous had previously been withdrawn. After the injection the animal was placed with the injected eye uppermost, and tonometric readings were made every ten minutes. Observations were made from time to time to ascertain whether the blood had been already coagulated. Six rabbits and 1 rhesus monkey were used in the experiments. The rabbits were killed one hour, twenty-four hours and two, four, five and sixteen days respectively after the injection.

RABBIT 42.—The animal was killed one hour after the injection. The anterior chamber was well filled with blood. Hypertension reached a high level, 85 mm., as shown in the curve (fig. 7).

Pathologic Changes (fig. 8).—The angle and the cilioscleral sinus, *Si*, were entirely filled with blood, but their normal arrangement was preserved. The sinus was distended on one side. The iris, *I*, was congested. The processes, *CP*, were swollen. The vessels, *V*, were dilated, especially the intrascleral and episcleral veins, *Ev*. However, no reaction or phagocytic migration had yet occurred.

RABBIT 39.—The animal was killed twenty-four hours later. There was chemosis of the limbus, which became severe about one hour after injection. The blood inside the chamber became blacker about one-half hour later, but it was not yet coagulated. An air bubble left inside still moved with the changing of the eye's position. The next day chemosis was still present. The hypertension, which reached 60 mm., fell to 40 mm. in twenty-four hours (fig. 9).

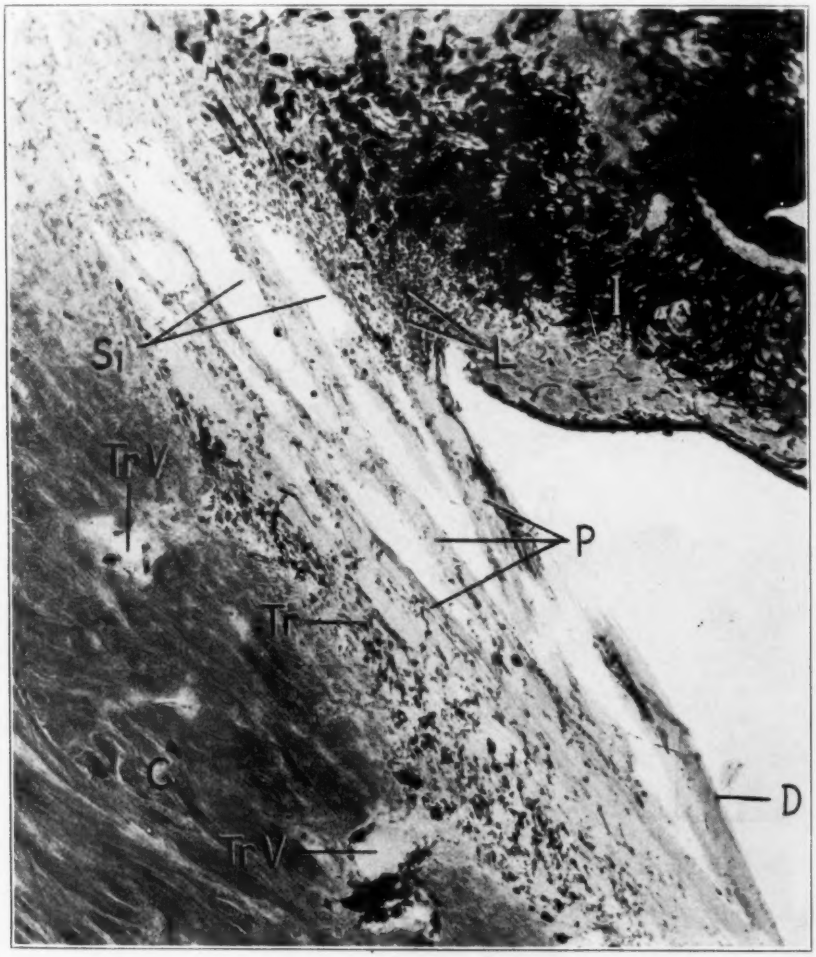

Fig. 6 (dog 1; left eye).—*P*, fanlike fibers of pectinate ligament; *L* clump of leukocytes.

Pathologic Changes (fig. 10).—The central portion of the cornea showed marked necrobiosis, the result of the high tension, which was similar to the condition observed in man. The cilioscleral sinus, *Si*, was occluded on both sides of the section by apposition of the base of the ciliary body, *BC*, and the root of the iris, *I*, against the sclera, *S*. This condition may be aptly designated as sinus synechia. The iris was greatly thickened, and its vessels were much dilated. Serum was present in the interstices of the stroma of the iris. The processes, *CP*, were greatly swollen. On the dependent side, blood had infiltrated between the sclera and the ciliary body. There was early proliferation of the endothelium, more pronounced in the cornea than in the iris, but little phagocytic migration. The

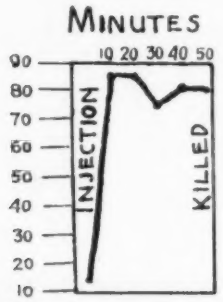

Fig. 7.—Tonometric curve for rabbit 42.

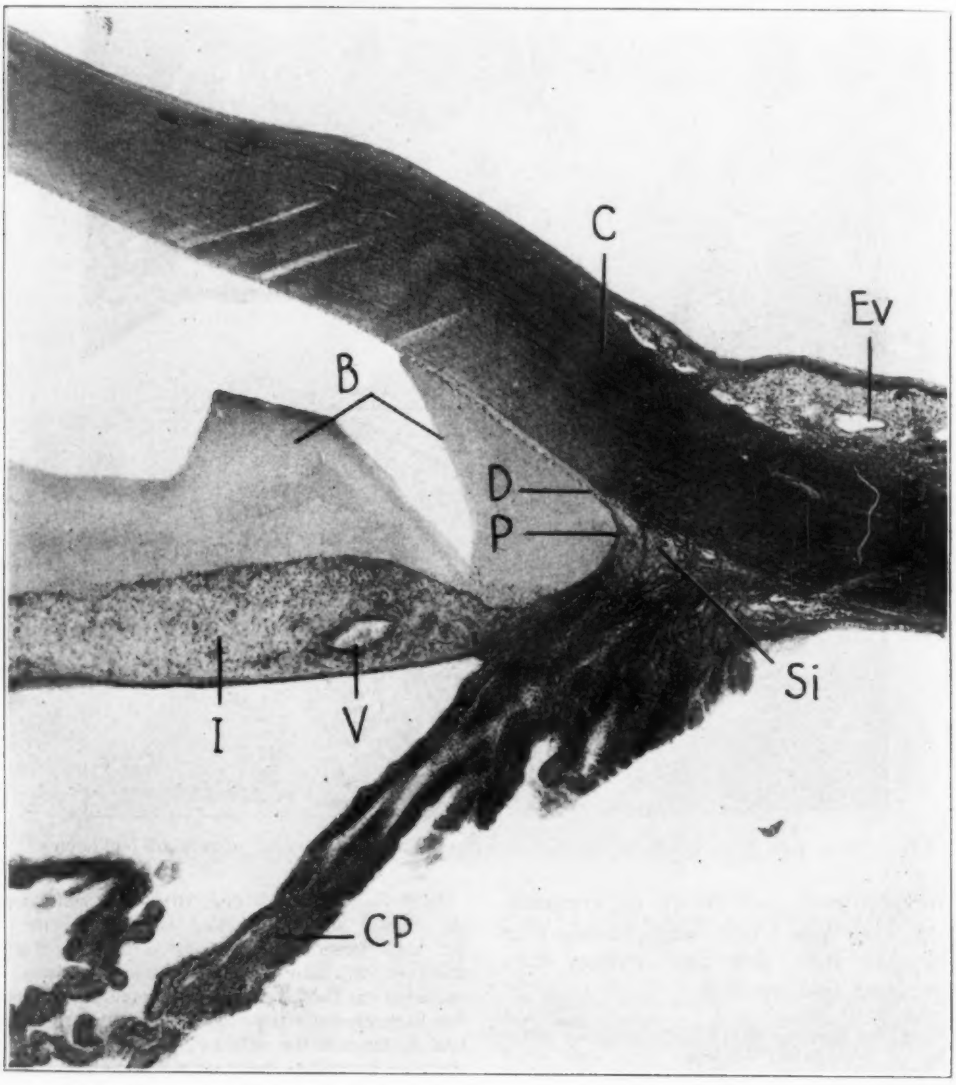

Fig. 8 (rabbit 42).—Response of injection of defibrinated blood into the anterior chamber. *B* indicates blood in the anterior chamber, which also fills the ciliosclera sinus; *D*, end of Descemet's membrane; *CP* ciliary processes, and *EV*, episcleral vessels.

corneal membrane had begun to dilate. The conjunctival and intrascleral vessels, *Ev*, were greatly dilated.

RABBIT 44.—The animal was killed two days after injection. The eye became congested and chemotic soon after the injection. The cornea began to dilate forty-eight hours later. A red and white clot was still present in the anterior chamber when the animal was killed. The tension reached the high level of 85 mm. but fell the next day to 45 mm. and was 35 mm. when the animal was killed (fig. 11).

Pathologic Changes (fig. 12).—The cornea, *C*, was much dilated at the limbus, and there was slight necrobi-

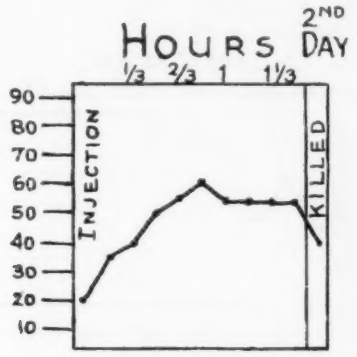

Fig. 9.—Tonometric curve for rabbit 39.

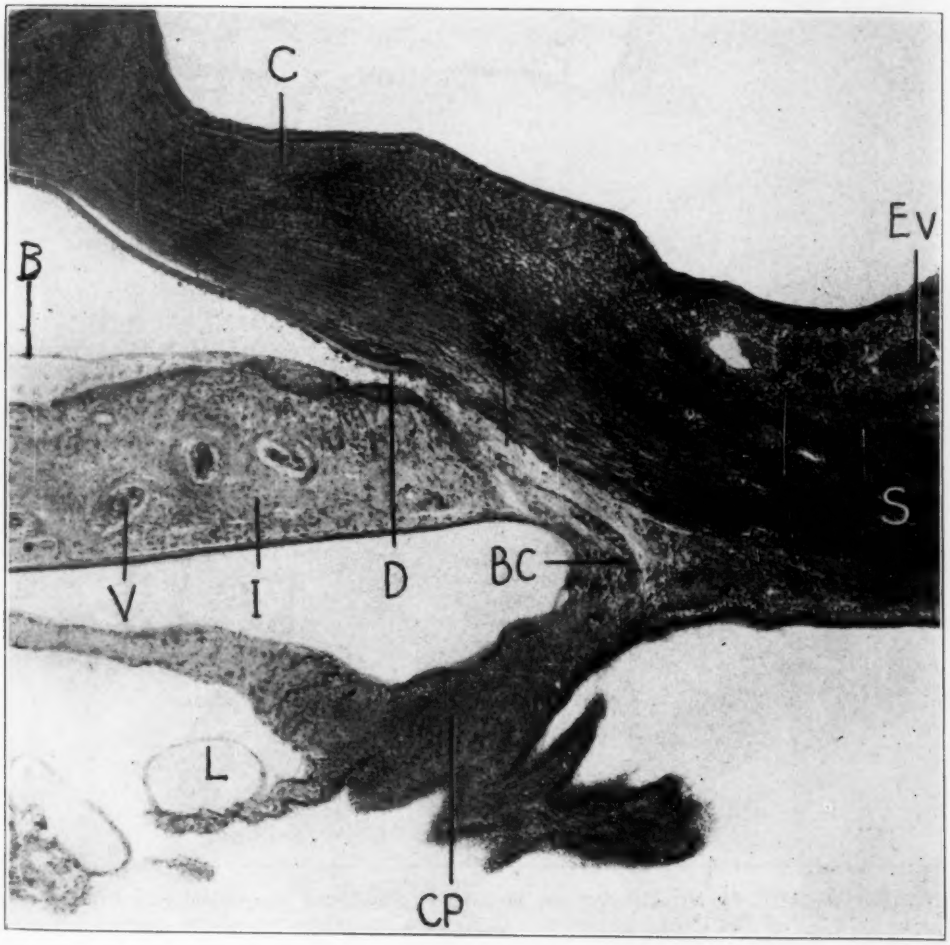

Fig. 10 (rabbit 39).—*B*, blood in the anterior chamber and on the surface of the iris; *I*; *Bc*, base of ciliary body; *CP*, ciliary processes; *L*, Graefe's blebs and *EV*, episcleral vessel.

osis, in the posterior lamella only. Blood, *Bl*, had infiltrated into the limbus. The sinus, *Si*, was partially infiltrated with blood and was occluded. On the dependent side the root of the iris, *Ir*, was thickened and

obstructed the sinus, which was partly filled with blood. The processes, *CP*, were greatly swollen, so that they pushed the root of the iris against the cornea and gave rise to a true anterior peripheral synechia. There was an enormous increase in the number of vessels in the iris, *V*, which were filled with leukocytes. Also present needle, and there was leaking of the blood when the needle was withdrawn. The eye, however, became congested and chemotic. The cornea was ectatic on the second day. Tension rose to 85 mm. and fell to 28 mm., continuing at the same level until the animal was killed (fig. 13).

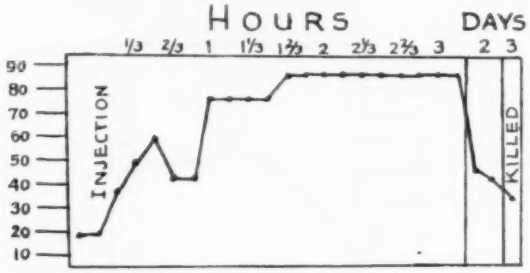

Fig. 11.—Tonometric curve for rabbit 44.

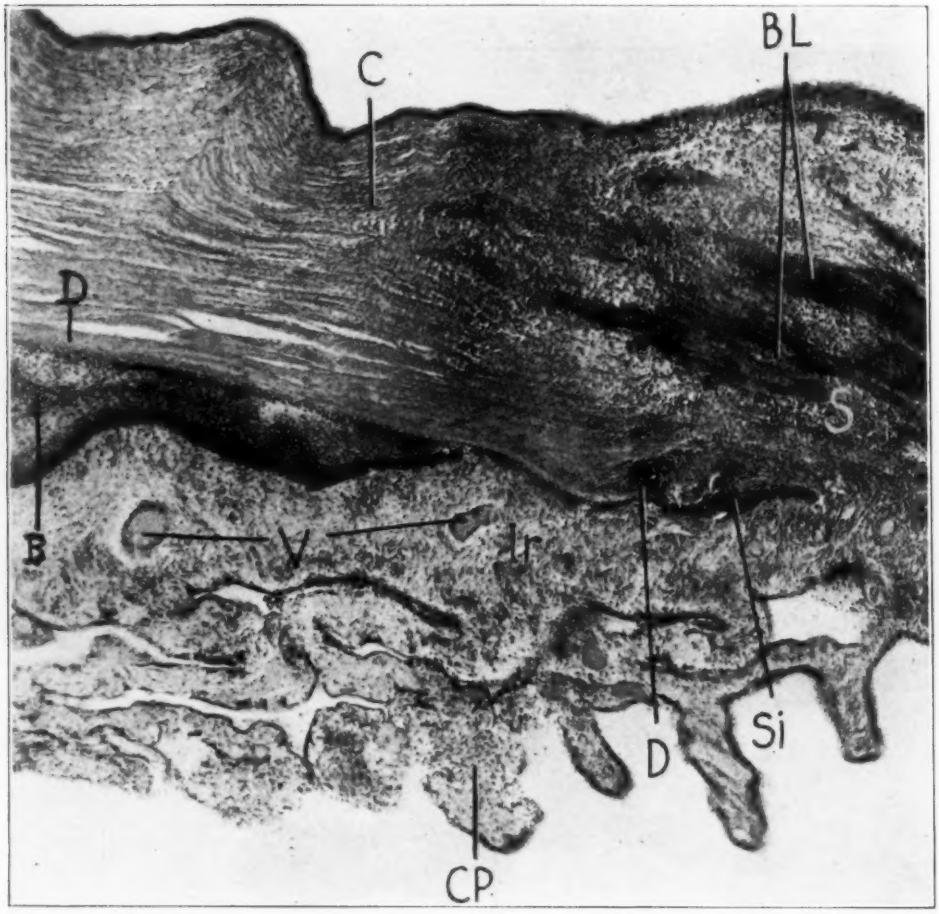

Fig. 12 (rabbit 44).—*BL*, blood infiltrating the limbus; *Si*, cilioscleral sinus, filled with blood; *Ir*, root of the iris, pushed forward by swollen ciliary processes, *CP*, forming an anterior peripheral synechia; *V*, vessels of the iris, and *B*, blood in the anterior chamber.

was notable proliferation of the corneal endothelium at the angle, due to irritation, and the leukocytic reaction was more prominent than in rabbit 39. There was a large amount of fluid outside the vessels.

Rabbit 45.—The animal was killed four days after the injection. Movements of the animal displaced the

Pathologic Changes (fig. 14).—The cornea, *C*, was considerably thicker in the center, due to edema. It was also ectatic. Four new blood vessels appeared, filled with granules of hemosiderin—some phagocytosed and some free—at the limbus and in the central portion of the cornea. The sinus, *Si*, was free on both sides. The

swollen root of the iris, *Ir*, was attached to the cornea at the end of Descemet's membrane, *D*, free communication with the anterior chamber being thus prevented. Blood was still present in the chamber. The iris, *I*, in the cornea. The processes, *CP*, were congested and in contact with the anterior surface of the lens. They seemed to be pushing the root of the iris outward. The choroid was not congested.

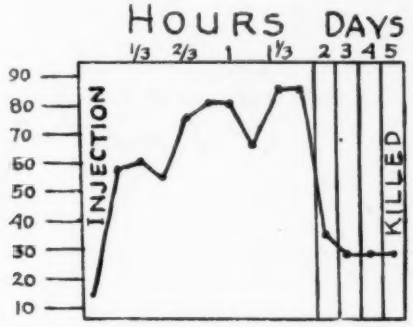

Fig. 13.—Tonometric curve for rabbit 45.

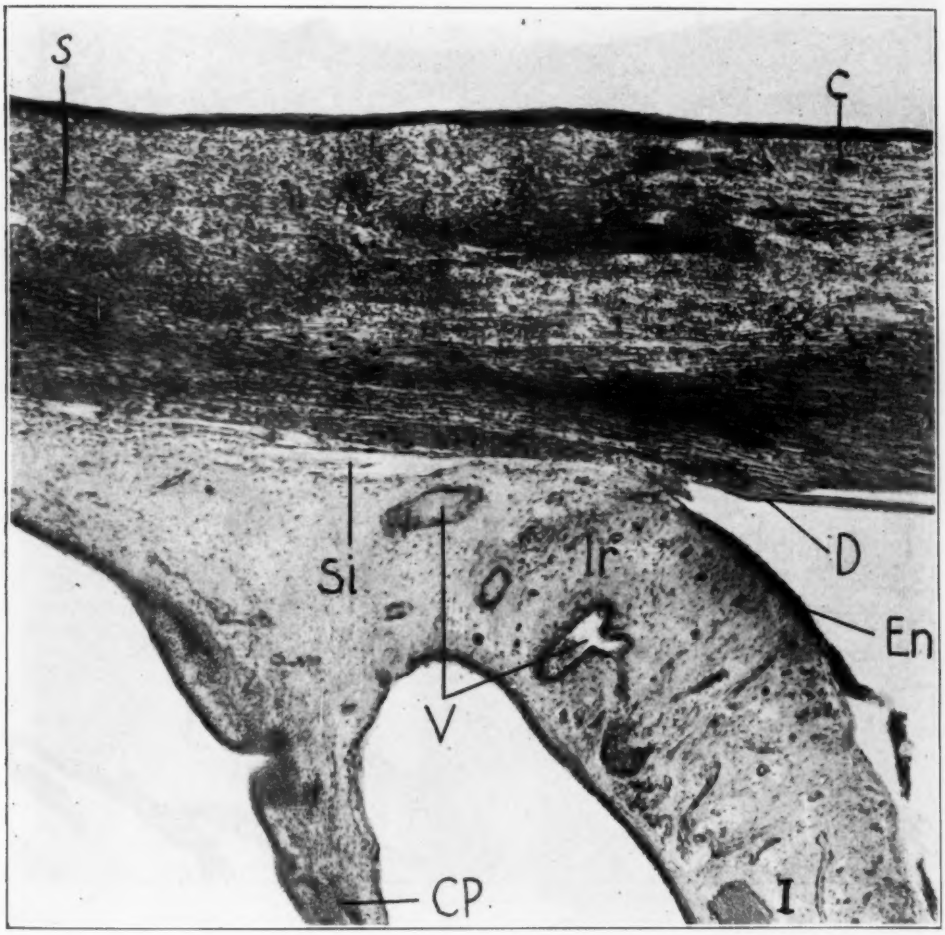

Fig. 14 (rabbit 45).—The abbreviations have the same meaning as in figure 12. *En* indicates endothelial proliferation over the surface of the iris.

was greatly thickened. There was still great vascularity, but the vessels, *V*, did not contain leukocytes, as in rabbit 44. Few leukocytes were present in the stroma of the iris. There was an increase in endothelial proliferation, *En*, and fibrous tissue in the iris, with less

RABBIT 36.—The animal was killed five days after injection. Two hours after the injection the eye was red and chemotic. The next day the cornea was clear, and the blood was absorbed over the iris but still remained over the pupil. A white clot or exudate lay

below and outside the pupil, reaching the angle. Tension attained a level of 85 mm. and lasted until the fifth day, when it was 30 mm. (fig. 15).

Pathologic Changes (fig. 16).—The eyeball was dilated as a whole, but the cornea was wrinkled. No necrobiosis of the cornea was present. A hemorrhage occurred near the limbus in the upper part. The sinus, *Si*, was filled up with fibrous tissue, *F*, which extended along the posterior surface of the cornea, between it and the iris, outside the peripheral synechia, *Psy*, and beyond it, as a result of organization of exudate. The iris, *Ir*, was less swollen. The vessels, *V*, were dilated, containing more blood. On the dependent side the same condition was present, but the iris had retracted and, detaching itself from Descemet's membrane, formed a pathologic angle. Endothelial proliferation occurred chiefly in the cornea, and to a less extent in the iris. The choroid was greatly congested.

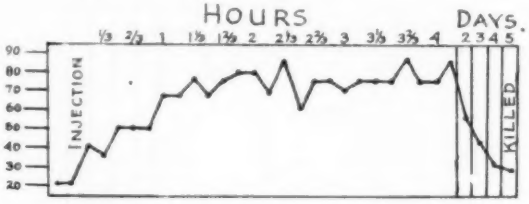

Fig. 15.—Tonometric curve for rabbit 36.

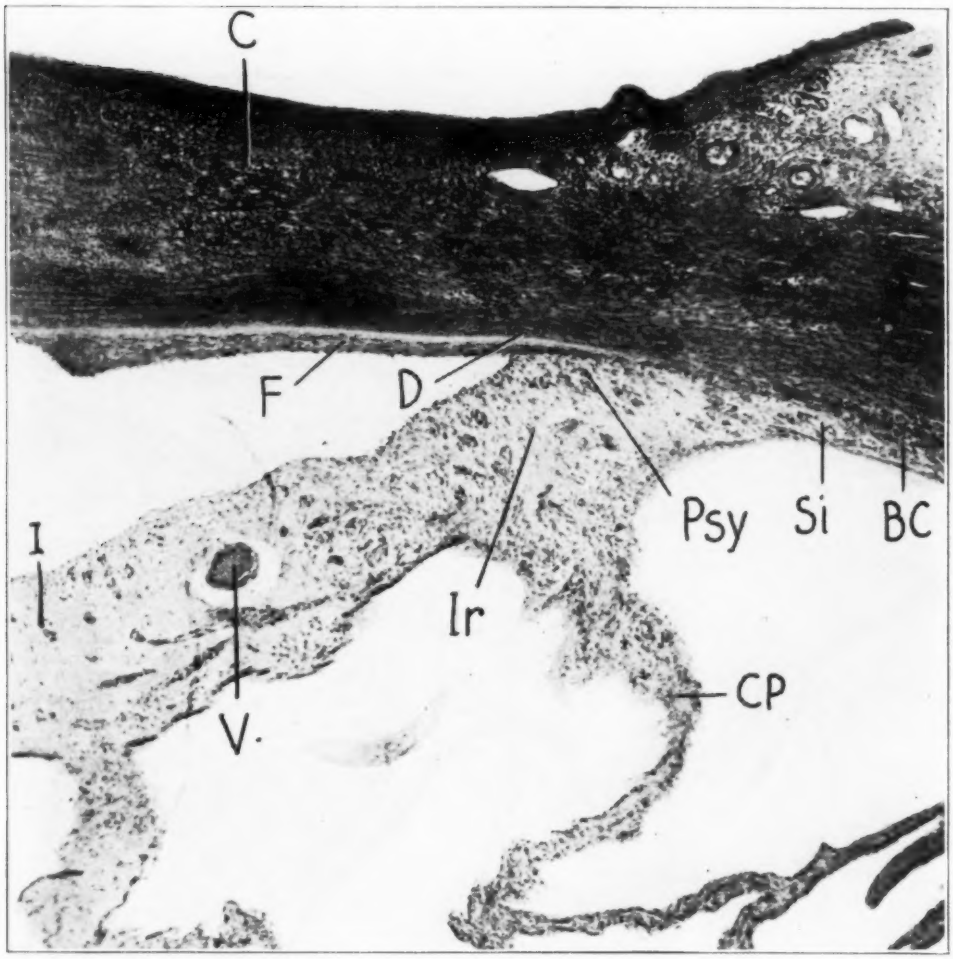

Fig. 16 (rabbit 36).—*BC* indicates base of ciliary body; *Ir*, root of iris, pushed forward; *Psy*, anterior peripheral synechia; *F*, fibrous tissue, forming a wedge between Descemet's membrane and the synechia; *I*, iris, with its vessels, *V*, greatly congested, and CP, ciliary processes.

Rabbit 37.—The animal was killed sixteen days after the injection. Chemosis was present at the end of the first hour. The next day the blood still covered the iris. The pupil, however, was visible. The cornea was slightly opaque and injected. Five days later the blood had become almost entirely absorbed in the anterior

chamber and over the iris. The pupil was dilated, non-active and irregular. New vessels were present on the surface of the iris. On the sixteenth day, when the animal was killed, the anterior chamber became shallow. Tension, which reached 85 mm. after injection, fell to 30 mm. the next day and remained so for the entire period of the experiment (fig. 17).

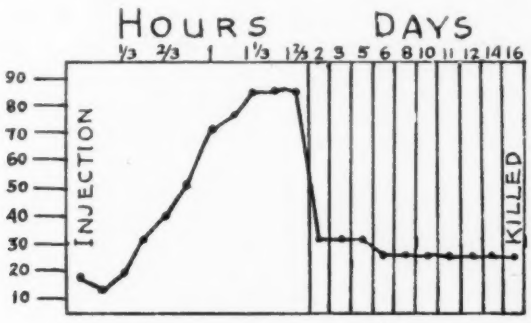

Fig. 17.—Tonometric curve for rabbit 37.

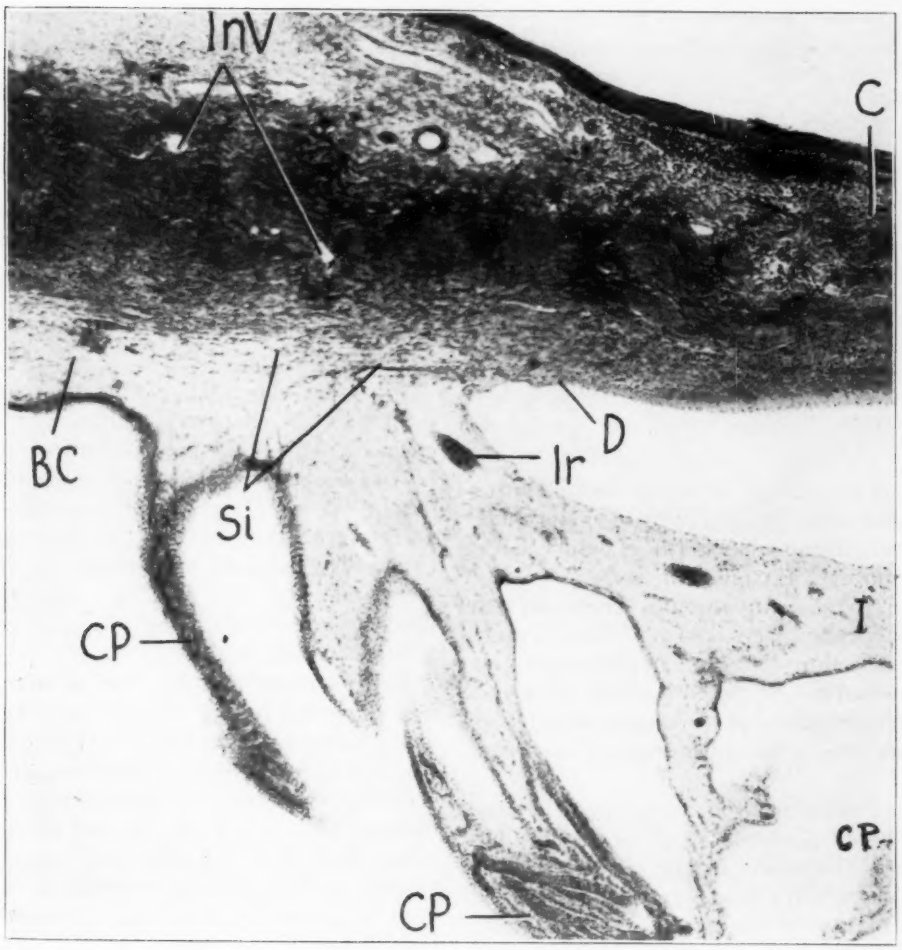

Fig. 18 (rabbit 37).—*InV*, intrascleral vessels; *BC*, base of ciliary body; *Ir*, root of the iris; *D*, end of Descemet's membrane, and *CP*, ciliary processes.

Pathologic Changes (fig. 18).—The cornea, *C*, showed newly formed vessels, containing leukocytes. No trace of blood was present in the anterior chamber. The sinus, *Si*, was closed by the root of the iris but still showed a few open spaces. The root of the iris, *Ir*, was retracted from the end of Descemet's membrane, *D*, by fibrous tissue. The iris, *I*, was still thicker near the pupil but was thinner and more atrophic at its base. The whole base of the ciliary body, *BC* was atrophic, although some processes, *CP*, were still swollen. Numerous dilated vessels showed sclerosis of their

walls. The choroid was enormously congested. The intrascleral veins, *In V*, were also greatly congested.

RHESUS MONKEY 1.—The right eye of this animal was given an injection first and the left eye twenty-four hours later. The animal was killed five and a half hours after the injection into the left eye.

Left Eye.—Chemosis started in the left eye a half-hour after the injection. Four hours later the iris became visible, the blood being rapidly absorbed from the angle to the center. After five and a half hours there was still blood in the chamber. Tension reached 67 mm. and fell to 58 mm. when the animal was killed (fig. 19).

Pathologic Changes (fig. 20).—The animal was killed five and a half hours after the injection. The left eyeball was greatly dilated; it was triangular, with the cornea at the apex. The anterior chamber was deep. There was blood in the angle, filling the trabecula, *Tr*, which with the canal of Schlemm, *Sch*, had preserved its normal aspect. The iris was edematous; the vessels were dilated, and the choroid was ectatic. No reaction had yet occurred.

Right Eye.—In the right eye, immediately after injection, the blood filled the anterior chamber, and there was slight chemosis. Two hours later the pupil became visible. One day later the chemosis was greatly increased. The blood in the anterior chamber was absorbed at that time. Tension rose to 80 mm., with oscillations, and the next day fell below normal (fig. 21).

Pathologic Changes: The changes were similar to those observed in the left eye. The cornea was normal. The eye was dilated, with scleral, followed by choroidal, ectasia. Hemorrhage was present inside the limbus. In the angle, the trabecula was somewhat distorted, containing blood and partially narrowing the lumen of the canal of Schlemm on one side. The trabecula contained blood but no leukocytes. The iris was thickened and edematous. The vessels were congested and dilated, and the processes were normal. The tolerance of this eye is remarkable as compared with the eye of the rabbit.

Résumé of Pathologic Observations.—During the first hour after the injection of defibrinated blood in the anterior chamber, the fluid entirely filled the ciliioscleral sinus on both sides and produced a great neurovascular response, but with no phagocytic reaction as yet. Ten minutes after the injection extreme hypertension appeared (measuring 85 mm.), which was due to the mechanical filling of the sinuses with blood. At this time there was no peripheral synechia (fig. 8).

At the end of twenty-four hours (fig. 10) the blood had beeen absorbed inside the sinus, but the enormous thickening of the root of the iris and the base of the ciliary body had produced mechanical closure of the sinuses. The angle of the chamber between the iris and the end of Descemet's membrane was open. As the intrascleral vessels, which normally absorb the greater part of the aqueous humor, were covered by the root of the iris and the base of the ciliary body, no absorption of fluid could be produced This adhesion is a new form of peripheral synechia, which may be called sinus synechia. At this time the leukocytic reaction was considerable, and there was also early proliferation of the endothelium, both of the cornea and of the iris.

Forty-eight hours later (fig. 12), in addition to obliteration of the sinus, the root of the iris had encroached on the anterior chamber, covering the end of Descemet's membrane, which in the normal rabbit eye marks the limit of the chamber. A true anterior peripheral synechia was thus produced, undoubtedly due in great part to the swelling and thickening of the processes, which pushed the root of the iris, and even part of its surface, against the cornea. The anterior chamber became shallow as a result of this pressure. The two reactions, leukocytic and endothelial, were pronounced. There was also a large amount of fluid outside the vessels.

Four days later (fig. 14) the small amount of blood injected had been absorbed on the sinus, which could be seen to have partly reopened. However, hypertension was still present, as a result of the adhesion of the root of the iris to the sclera, which cut off the communications between the anterior chamber and the sinus. The iris and processes were greatly swollen and the vessels in the iris much dilated, but they did not contain as many leukocytes as at the end of twenty-four hours. On the other hand, the endothelial reaction had increased. There were endothelial proliferation and formation of fibrous tissue in the iris.

Five days later (fig. 15) the most striking symptom was the great dilatation of the whole eyeball. The sinuses were entirely filled with fibrous tissue, the result of organization of exudates. A true peripheral synechia was also present, the root of the iris covering a great extent of Descemet's membrane. The iridic membrane was less swollen. Endothelial proliferation continued chiefly in the cornea and to a less extent in the iris.

Sixteen days later (fig. 18) no trace of blood was observed in the anterior chamber. There was a sinus synechia but no peripheral synechia, the iris being retracted from the end of Descemet's membrane by the formation of fibrous tissue. The root of the iris and the base of the ciliary body were atrophic—a retrograde process similar to the condition seen in the human eye with long-standing glaucoma. However, at the end of two weeks there was still congestion of the eye.

The eye of the rhesus monkey (fig. 20) presented a different reaction to the injection of blood than did the rabbit eye. The absorption was so rapid that at the end of five and a quarter hours little blood was left in the chamber. Some

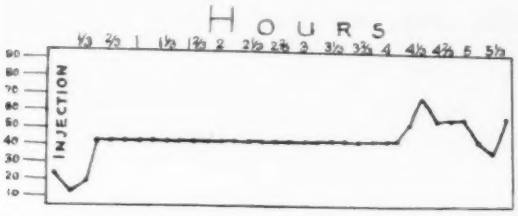

Fig. 19.—Tonometric curve for left eye of rhesus monkey 1.

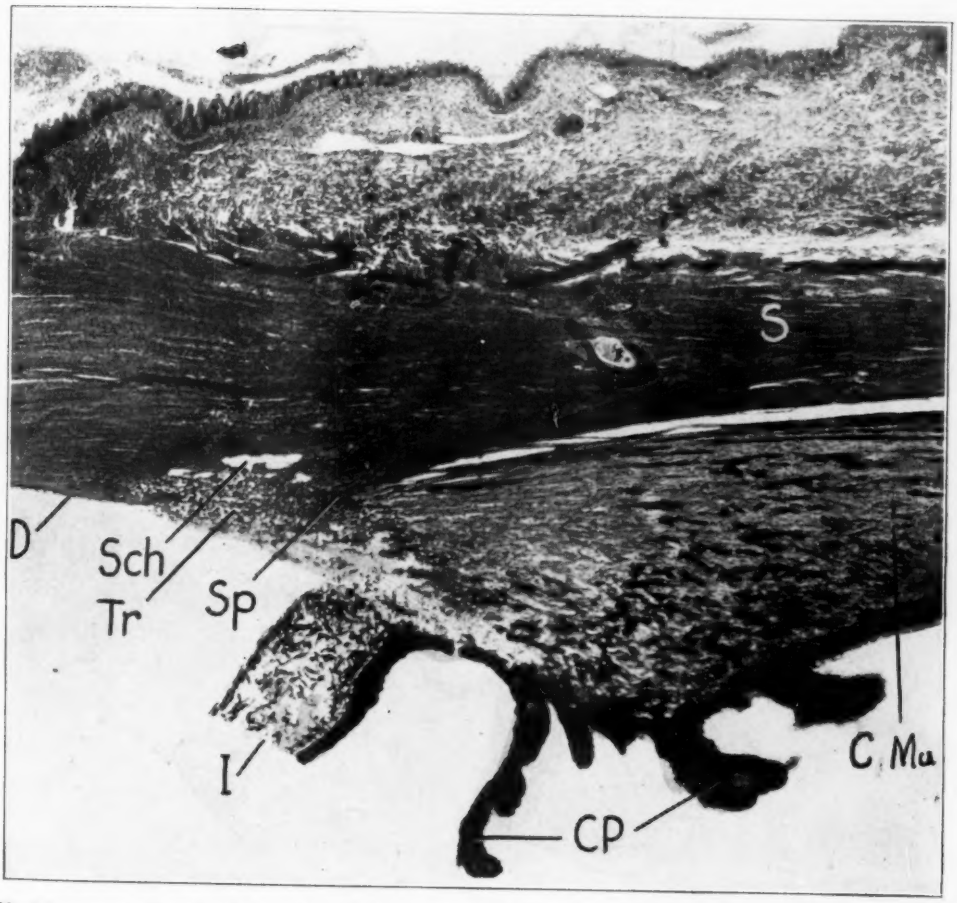

Fig. 20 (rhesus monkey 1; left eye).—*Sch.* canal of Schlemm; *C Mu,* ciliary muscle; *CP,* ciliary processes, *Sp,* scleral spur.

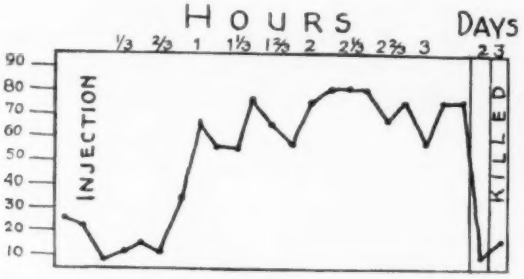

Fig. 21.—Tonometric curve for the right eye of rhesus monkey 1.

corpuscles filled the trabecula, which, with the canal of Schlemm, had a normal structure. Still, tension reached nearly 70 mm. The iris was edematous, with a great number of dilated vessels, but there was no leukocytic reaction. In the other eye, after forty-eight hours the dilatation of the whole eyeball was extreme. The tension increased more rapidly than in the rabbit. Tension had fallen to normal, although the trabecula was somewhat disturbed and the canal of Schlemm narrowed. The leukocytic reaction was slight. The iris was thickened and edematous, with congested vessels. The tolerance of this monkey's eye to the injection of blood was remarkable.

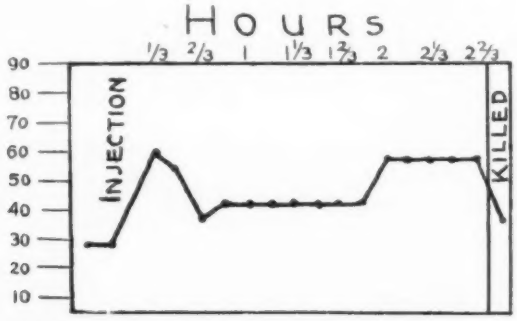

Fig. 22.—Tonometric curve for rabbit 30.

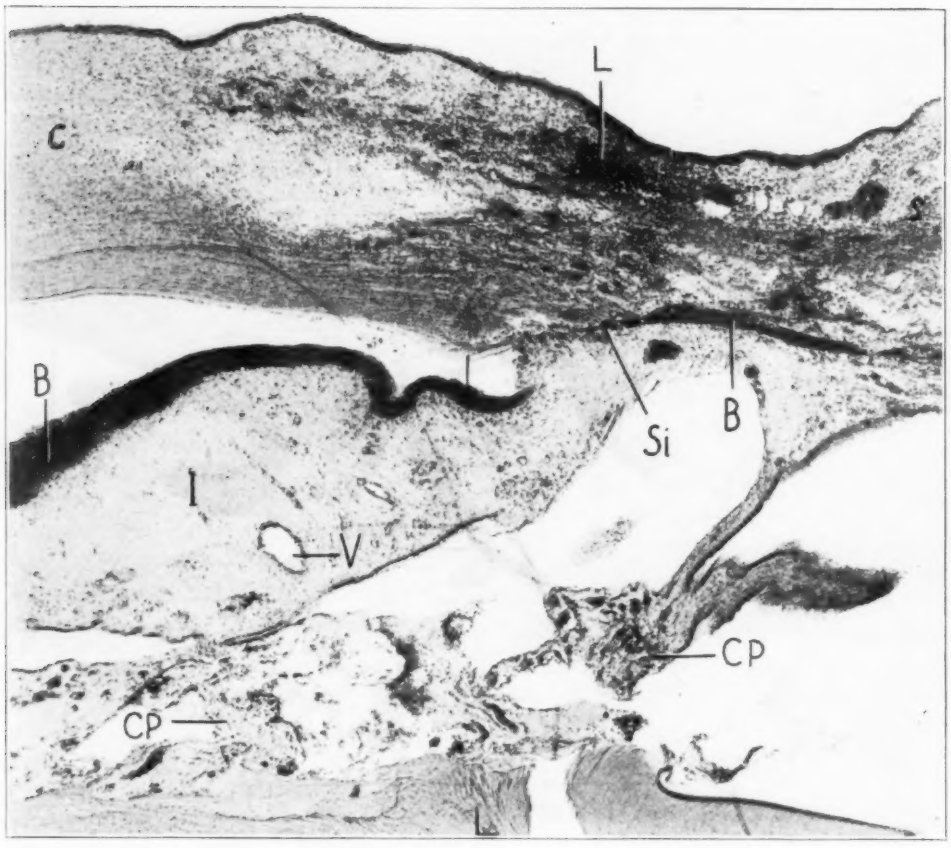

Fig. 23.—*L*, clump of leukocytes; *B*, blood filling the sinus and infiltrating the sclera and subchoroidal space; *I*, iris, covered with blood, *B*; *V*, dilated vessel in the iris; *CP*, ciliary processes, and *L*, lens.

The dilatation of the cornea and of the whole eyeball in animals usually produces a rapid descent in intraocular pressure on the second or the third day. It is probable that if the sclera were as resistant as it is in man, a condition

which clinically and pathologically resembled glaucoma in man would be produced.

EXPERIMENTS WITH PURE BLOOD

The anterior chamber was emptied by the withdrawal of the aqueous with a fine needle and the chamber. After the injection the animal was placed at rest on the side opposite that of the eye operated on. Reaction did not usually appear until fifteen or twenty minutes had elapsed. When the injected blood filled the anterior chamber under pressure, the cornea became

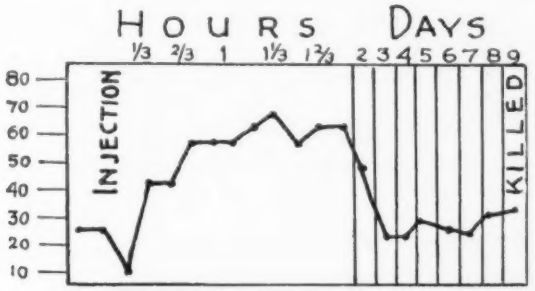

Fig. 24.—Tonometric curve for rabbit 29.

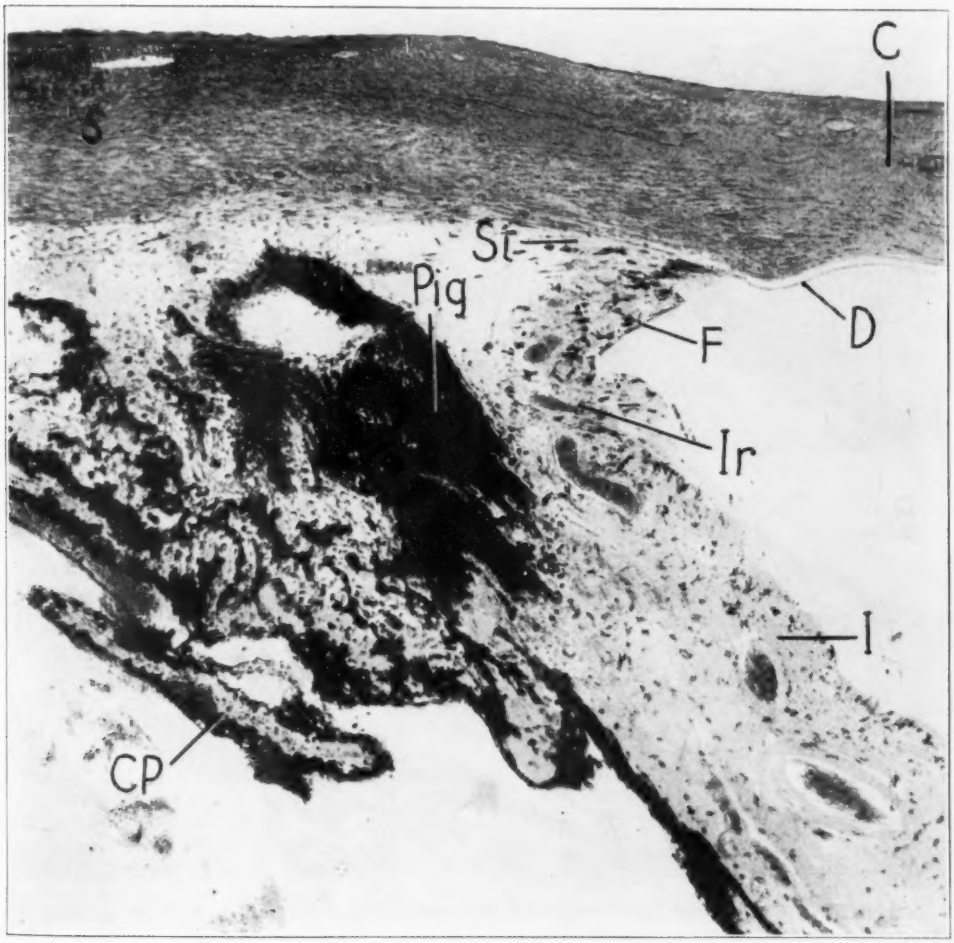

Fig. 25 (rabbit 29).—*F*, fibrous membrane, covering the root of the iris, *Ir*, and *Pig*, collection of pigment.

syringe. The syringe was then removed and the needle kept firmly in place. Another syringe, filled with blood taken directly from the heart of the rabbit, was connected with the needle in

opaque and the eye red and chemotic. In 1 rabbit the eyeball burst at the end of ten days, after a large scleral staphyloma had developed. Microscopic section showed a large hemorrhage

in the vitreous and under the choroid. When the injection was made slowly and the pressure was gradually increased, the cornea kept its transparency. The blood apparently clotted in the anterior chamber about half an hour after injection. The tension started to rise ten minutes later, usually reaching a height of 65 to 80 mm. Hypertension lasted for two and a half hours or more, but the next day the tension was much lower and returned to normal, or even below normal. After twenty-four hours the dilation of the cornea and the anterior portion of the eye began. In one week the eye became quiet and redness disappeared, but the anterior segment remained permanently ectatic. Injections were made in 4 rabbits, and the animals were killed twenty-four hours and nine, ten and twenty-three days later.

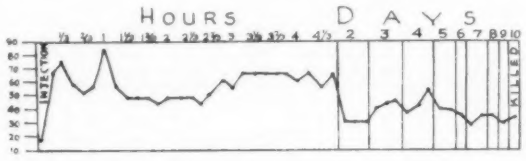

Fig. 26.—Tonometric curve for rabbit 28.

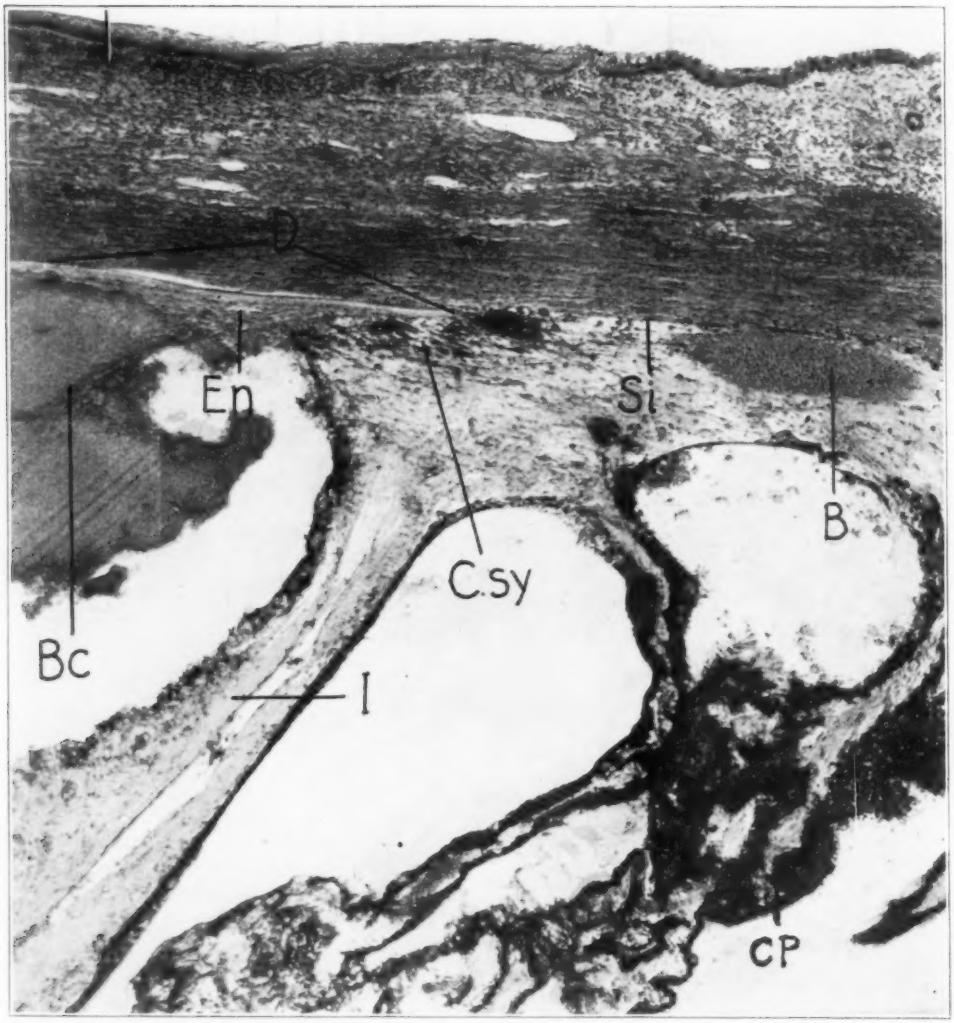

Fig. 27 (rabbit 28).—*Csy*, iridocorneal synechia; *En*, endothelial proliferation, forming a mass between the cornea and the iris and extending in strands around the clot, *BC*.

Rabbit 30.—The animal was killed twenty-four hours after injection. The eye became red and chemotic.

Tension, as shown by the curve (fig. 22), reached a height of 55 mm. and had fallen to 40 mm. two hours later. The next day the eye was congested and the cornea dilated and hazy. The anterior chamber was filled with blood.

Pathologic Changes.—The cornea was edematous. Leukocytes were noted superficially at the limbus. New blood vessels had formed inside the cornea. The anterior chamber showed a thick layer of blood filling the sinus on the dependent side. Blood also infiltrated the ciliary body, reaching the ora serrata. On the other side of the angle (fig. 23), the sinus, *Si,* was filled with blood, *B,* and was occluded by the root of the iris. Beyond, there was a slight infiltration of blood into the ciliary body. The iris, *I,* and processes, *CP,* were greatly congested, and the blood vessels, *V,* were dilated. There was blood over the surface of the iris, *B,* and in the posterior chamber. The lens, *L,* was injured. There was a slight subchoroid hemorrhage. In the iris dispersion of pigment was apparent.

Rabbit 29.—The animal was killed nine days after injection. Chemosis started in the conjunctiva fifteen minutes after the injection and became severe one and a half hours later. Tension reached 65 mm. and fell the next day, but remained higher than normal (fig. 24). Twenty-four hours later chemosis was still present. The blood in the chamber was reduced to hyphemia, with downward extension. Red coloration of the iris was apparent for four or five days. At that time the cornea appeared dilated, ectatic and hazy, and there was a white exudate in the angle. Seven days later the cornea had regained its transparency; but there was still blood in the anterior chamber, and the anterior staphyloma had increased. The animal was then killed.

Pathologic Changes (fig. 25).—The cornea was edematous and thickened. The anterior chamber was deep and contained sparse, individually distributed blood cells. A fibrous membrane, *F,* covered the iris near the angle. The sinus, *Si,* was occluded in front by a sinus synechia up to the end of Descemet's membrane, *D,* but opened backward on each side. There was no peripheral synechia. The iris, *I,* was thick, with dilated blood vessels. The processes, *CP,* were thickened and were adherent to each other. The pigment epithelium, *Pig,* showed great disturbances, with enormous collections in the ciliary body. There were subchoroid hemorrhage and detachment of the choroid.

Rabbit 28.—The animal was killed ten days after injection. Fifteen minutes after the injection chemosis appeared around the limbus; one-half hour later the blood was seen clotting in the anterior chamber, and the clot began to retract. Two hours later chemosis was pronounced. The lids were slightly swollen, and there was a watery discharge from the eye. Tension, which had reached a high level (90 mm.), fell the following day to 35 mm. (fig. 26). At that time chemosis was still present, the cornea being hazy and insensitive. In the anterior chamber the clot had retracted to a brown mass. Seven days after the injection the eyeball was dilated, and an anterior staphyloma of the limbus extended inward and downward. Blood clots were still visible in the anterior chamber over the iris and in the angle. The animal was killed, with the tension still high (35 mm.).

Pathologic Changes (fig. 27).—No necrobiosis of the cornea was evident. There were a sinus synechia, *Si,* with the spaces back of it filled with blood, *B,* and iridocorneal synechiae, *Csy.* These extended beyond the end of Descemet's membrane, *D,* and were broad and permanent. Adjacent to them proliferation of corneal endothelium, *En,* formed a mass over the blood clot, *BC.* In the anterior chamber the endothelium was transformed into strands around the clot. The iris, *I,* was thickened as a result of increase in and dilation of the vessels. Greefe blebs were visible in the process, such as are produced in man by hypotension. The pigment epithelium was disturbed and collected in masses in the processes.

Rabbit 1.—The animal was killed twenty-three days after injection. This animal received two injections of blood. The first one was not successful, as blood came out through the corneal puncture. However, the tension rose to 60 mm. and returned to normal on the next day. The second injection was made six days after the first, and the tension rose to 40 and 50 mm. (fig. 28). The eye remained red, and there was some edema of the lids. The cornea appeared hazy and chemotic. At the end of three days the eyeball became dilated, so that the anterior chamber was deep. Blood remained in the anterior chamber for eighteen days, but was already absorbed on the twenty-third day, when the eye was removed.

Pathologic Changes (fig. 29).—The cornea, *C,* was greatly dilated, and the posterior corneal lamellas were necrobiotic. The sinus was entirely occluded on both sides. The iris, *I,* was atrophic and had receded backward from the end of Descemet's membrane. The processes, *CP,* were also shrunken. Blood, *B,* and hematogenous pigment were present within the synechia, which was fibrous and permanent. The cornea was greatly dilated, and the anterior chamber was deep.

Résumé of Pathologic Changes.—The reaction of the eye with pure blood was somewhat different than with defibrinated blood. The blood apparently clotted in the anterior chamber about one-half hour after the injection and spread over the surface of the iris. It was not possible to study, as with defibrinated blood, the early cause of hypertension, since the first rabbit was killed twenty-four hours after injection. In this animal (fig. 23) the ciliioscleral sinuses were filled with coagulated blood, which on one side reached the ora serrata and on the other trickled into the posterior chamber. The edema of the iris was enormous, probably more than with defibrinated blood; the ciliary body itself was swollen, and a sinus synechia had already developed through complete obliteration of the sinus cavity. The great increase of tension in this eye was essentially due to this mechanical occlusion of the sinus by the blood and by the edema of the base of the ciliary body.

In rabbit 29, after nine days (fig. 25) the cornea was greatly dilated, edematous and thickened. Sinus synechiae, but no peripheral synechiae, existed. The anterior chamber became deeper, an alteration which prevented the processes from pushing the root of the iris against the cornea and accounted for the small peripheral synechiae in rabbit 28 (fig. 27). In this animal the proliferation of the corneal endothelium was extreme, not only at the angle but in strands around the clot remaining in the anterior chamber.

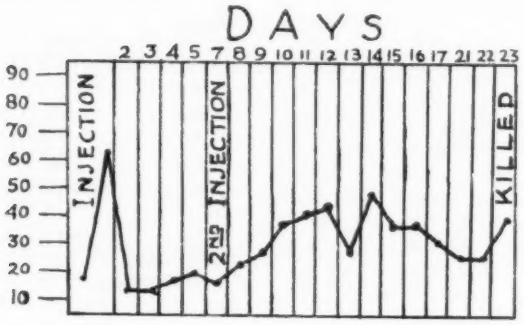

Fig. 28.—Tonometric curve for rabbit 1.

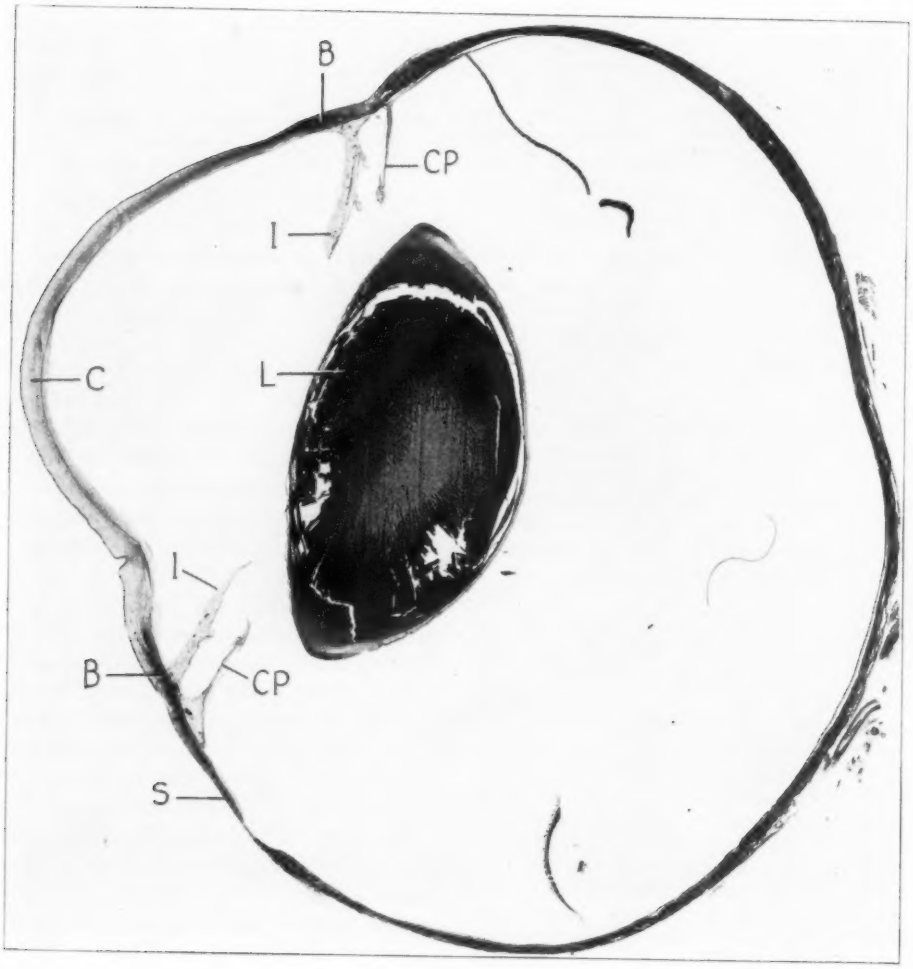

Fig. 29 (rabbit 1).—*B*, blood and pigment collected inside the sinus synechia; *CP*, atrophic ciliary processes, and *L*, lens.

It is my impression that with pure blood the dilation of the whole eyeball was greater than with defibrinated blood.

The late results of hypertension were clearly seen in rabbit 1 (fig. 29), which was killed twenty-three days after the injection. As in man, the iris and ciliary body became atrophic and receded backward. The sinus synechia thus became permanent. A new angle of the chamber was formed posteriorly. These retrograde changes were similar to those observed in patients with long-standing glaucoma.

COMMENT

If the changes produced by the injection of serum into the anterior chamber are compared with the reactions to defibrinated blood and pure blood, the first thing observed is that with serum hypertension started twenty-five minutes after the injection, while with defibrinated blood the increase of tension became manifest within ten minutes after the injection and remained at a high level during periods of from one hour to one day. In the rabbit in which serum was injected, as in the rabbits which received defibrinated blood, the intraocular tension increased even when no sinus synechia or true peripheral synechia had been developed. This was due to three factors.

1. The chemical composition of the aqueous became colloidal, the change considerably disturbing the absorption through the trabecular veins at the external wall of the sinus. This great increase in colloids in the aqueous produced an inversion of the normal current, the colloidal aqueous sucking fluid from the intrascleral vessels.

2. The filling of the sinus with serum or blood, and later with fibrin, mechanically prevented the normal aqueous in the anterior chamber from reaching the trabecular vessels on the surface of the sclera, the obstruction hindering the outflow of fluid and immediately promoting a great increase of intraocular tension.

3. The neurovascular response to hypertension was entirely different with serum than with blood. With serum the response was especially conspicuous in the iris, while with defibrinated blood the response was greater in the processes and base of the ciliary body. With the serum the iris underwent great vasodilation. This, in turn, increased the permeability of the walls of the veins and the capillaries, through which a larger amount of serum passed and infiltrated the stroma of the iris, which became thicker. The sinus was filled with serum and leukocytes. After two days the chamber became shallow. There was an endothelial reaction, with resulting attachment of the surface of the iris to the cornea and beginning production of a true anterior peripheral synechia.

With defibrinated blood the response was different. It was not limited to the iris but extended especially to the ciliary processes. These processes became edematous and swollen. The base of the ciliary body behind the processes also became edematous, increased in thickness and pushed the inner wall of the sinus outward, producing a mechanical closure of the cavity of the sinus. To this closure I have given the name "sinus synechia," as opposed to anterior peripheral synechia, which is produced by the adhesion of the surface of the root of the iris to the corneal limbus. The sinus synechia in animals corresponds to the anterior peripheral synechia in man, as in lower mammals the sinus is the principal channel for the outflow of the intraocular liquid. The sinus synechia usually did not develop until forty-eight hours after the injection. Later, the increased thickness of the root of the iris made the anterior chamber shallower, and the swollen processes pushed the root of the iris against the cornea. This entirely sealed the sinus and prevented the flow of aqueous into its cavity.

Besides this mechanical occlusion of the sinus, one must consider the action of the blood corpuscles, which act as a foreign body. They produce a greater neurovascular reaction than that to serum. Phagocytes migrate from the vessels in larger numbers and infiltrate all the structures around the sinus and fill its cavity. The endothelium then proliferates, as a result of irritation, producing bands of tissue which attach the root of the iris to the cornea, first temporarily and then permanently.

With pure blood conditions differed from those with defibrinated blood. The blood coagulated in the anterior chamber and the sinus, occluding the latter and coating the walls of the anterior chamber. Usually with pure blood hypertension lasted longer. The edema of the iris and the ciliary processes was greater, and the sinus synechia was already present at the end of twenty-four hours. The neurovascular response was more active than that with defibrinated blood. The whole blood, acting as a foreign body, produced an increase in the amount of liquid, made the anterior chamber deeper and so prevented the peripheral synechia from becoming wider. The endothelial reaction was also more intense, strands forming at the angle and around the clot in the chamber. The dilation of the cornea and the whole eyeball occurred earlier and was more pronounced.

Undoubtedly, chemical changes in the blood increased the irritation and led to the formation of lytic enzymes, which helped phagocytosis and the process of absorption of the blood. They have not been considered in this paper. The reader is referred to the work of Freund and Lustig,[11] Kikai and Riehm.

The responses elicited by injection of blood into the anterior chamber may be summarized as follows:

Mechanical.—When the angle is filled with blood, clot and fibrin, the aqueous is prevented from contact with the walls of the trabecular veins or the canal of Schlemm.

Physical.—The aqueous is laden with a large amount of proteins. These reverse the normal osmotic direction of fluid currents, attracting fluid from the vessels.

Chemical.—Chemical changes are produced in the blood injected into the anterior chamber by several reactions and ferments, e. g., by irritation and production of lytic substances.

Vital.—These include: 1. Sympathetic and parasympathetic stimulation, with dilation of the blood vessels, ophthalmotonic reaction and hypertension.

2. Neurovascular response, a defense reaction which produces dilation first of the vessels of the iris and then of the vessels in the ciliary body and the sclera, for the absorption of the excess of fluid and clearing of obstruction.

3. Increase in permeability of the walls of capillaries and veins.

4. Migration of leukocytes from the surface of the iris, the ciliary body and the scleral plexus for phagocytosis of foreign material.

5. Irritation of endothelial cells in the cornea and iris by proteins (?) and chemical substances.

6. Production of sinus synechia and peripheral synechia, first by contact and then by formation of fibrous connective tissue.

7. Great dilation of the eyeball in animals, similar to hydrophthalmos in children.

8. Retrograde changes, such as atrophy of the iris and ciliary processes and permanent peripheral synechiae.

CONCLUSIONS

Experiments made on rabbits, dogs and monkeys to observe the development of peripheral synechiae in conditions of increased intraocular tension show that the first step in the production of this increased tension was not the mechanical obstruction of the channels of outflow (cilioscleral sinus in lower mammals, trabecula and canal of Schlemm in monkeys) by the base of the ciliary body and the root of the iris, but a disturbance in the normal outflow of aqueous, which produced immediate hypertension. This, in turn, with the normal response of tissues by vasodilation and edema, produced a large swelling of the base of the ciliary body, which obliterated the cilioscleral sinus, with resulting adhesion (sinus synechia), and swelling of the processes. The thickened processes pushed the root of the iris forward, made the anterior chamber shallow and produced an anterior peripheral synechia.

The experiments consisted of injections of serum into the anterior chamber, as well as injections of pure and defibrinated blood, the use of substances foreign to the organism being avoided. Unfortunately, there is no other reliable method of producing experimental glaucoma.

Dr. Algernon B. Reese cooperated in the pathologic interpretation of the microscopic slides of the eyes operated on, and Dr. Edward Gallardo helped in the operations and the follow-up observations on the animals.

11. Freund, E., and Lustig, B.: Ueber die Muttersubstanz des im Blut und Muskel entstehenden Ammoniaks, Biochem. Ztschr. **240**:326, 1931.

APPRAISAL OF VALUE OF AN ORTHOPTIC CLINIC IN PRIVATE PRACTICE

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The Memphis Orthoptic Clinic, available to all ophthalmologists in that city, has been in operation for the past ten years. It was organized in a frank spirit of skepticism; because of this feeling, its facilities have been available to patients without special reference to expense, this provision allowing the ophthalmologists of the city to refer to it patients with any type of muscular condition for treatment for as long as seems desirable. We have studied the records of the clinic to determine whether it has justified its existence.

In the last five years, 958 patients were seen at least once for examination and diagnosis, with a large number of whom members of the staff were able to maintain personal contact. Of the latter number, 345 were found suitable for orthoptic training and have come at varying periods for such training. For the past year, the two groups, the patients who remained under observation and those who received orthoptic training, numbered 389 and 334 respectively, the growth indicating a healthy increase, appreciation of what an orthoptic clinic can do for private patients. At present, the clinic has 53 patients who are given regular office treatment for half-hour periods, three times a week.

The clinic is operated by two trained technicians, of whom one (J.S.R.) is certified by the American Board of Orthoptic Technicians. If space and talent were available, the number of attendants could well be increased.

USEFUL INSTRUMENTS

For the first step in orthoptic work, which is the diagnosis of the state of muscular balance the screen test with prisms, made for near and for distant vision and for the cardinal fields, is of prime importance. For the testing of fusion ability and projection, the most necessary piece of equipment is one of the major amblyoscopes. These include the synoptophore, the synoptiscope and the orthoptoscope. Of these, the synoptophore is the instrument with which we are most familiar at our clinic. Its adaptability and the clear view of the patient's eyes that it affords make an instrument of this type invaluable in actual treatment, as well as necessary in diagnosis. In its favor is the fact that it is not automatic, so that fine adjustments are facilitated. It is by means of the major amblyoscope that abnormal retinal correspondence is most easily detected, and it is with this instrument only that patients with this defect are treated binocularly.

A simple hand stereoscope should always be available for the development of fusion amplitude and stereopsis. With many manifest conditions it is of no use, and under no circumstances should it be employed when abnormal retinal correspondence is suspected. However, in a high percentage of cases in which orthoptic treatment is required, a stereoscope will be of value for both office and home treatment.

The junior metronoscope, equipped with rotary prisms, is an instrument which we have found to have many uses. We recommend it particularly for persons requiring treatment at reading distance; however, it is adaptable to other needs. Patients with convergence insufficiency are quickly benefited by prism reading. When suppression is suspected or is known to be slight, the metronoscope is made more useful by the addition of a reading bar. In cases of insufficiency the metronoscope has a real diagnostic value.

In our clinic we also make use of the following apparatus:

1. The standard phorometer with Risley prisms, plus a Project-O-Chart, for determination of muscular balance.

2. The stereo-orthopter, an automatic instrument with lateral motion, excellent for development of fusion amplitude and for training of stereopsis.

3. The Maddox cheiroscope, used in cases of suppression and those in which binocular coordination is true but weak.

4. The kinetic stereoscope, designed for rotary movement and guided by hand.

5. The Remy separator, a simple, easily made hand device for use in many cases of lateral imbalance.

6. A reading bar of the simplest design, which is of distinct usefulness in many cases of binocular imbalance in which voluntary control is being taught.

7. A red and blue filter, which is useful in recession exercises with a light and in cases of suppression in connection with the tracing of red drawings.

When one begins the examination of a patient, one cannot foretell that the trouble is muscular, since the symptoms vary so much; the routine tests should therefore at least be of such extent that any gross error is soon detected. These tests ordinarily consist in determination of visual acuity for far and near vision, a quick test with the screen and parallax, a measure of the near point of convergence and an estimate of the

Read at the annual meeting of the American Academy of Ophthalmology and Otolaryngology, Section on Ophthalmology, Chicago, October 1943.

muscular balance for 20 feet (6 meters) and 14 inches (36 cm.) with vertical prism or the Maddox rod. Usually correction of the refractive error, when that is indicated by the presence of faulty vision or symptoms, gives the desired relief. In cases of squint or of more than the normal amount of heterophoria, further tests of binocular vision, fusion ability and muscular strength (prism divergence and prism convergence) are made, and if the conditions seem to justify it, or if symptoms of asthenopia persist after a careful correction of the refractive error and wearing of the prescribed glasses, the patient is referred for further study in the orthoptic clinic. It would be easy to tax the resources of the clinic by sending more people there, but the plan we follow gives us a chance to estimate the need of such tests and saves the time of the clinic workers. In other words, we try not to call on the clinic for such information as we should properly and easily acquire with the equipment in the trial case, nor do we hope to have the clinic look after patients who need only proper refraction or some form of local or general medical treatment.

The role of orthoptics in the treatment of binocular incoordination is unique in that there is no substitute for the part that it plays. Just as refraction has its own place, so does orthoptic treatment. Realization that the miraculous cannot be accomplished by this comparatively simple procedure will lessen the disappointment of those whose expectations are too great.

We do not make extravagant claims concerning progress made in cases in which orthoptic treatment has been prescribed, but by cautious procedure we are gradually coming to more definite conclusions about the value of such treatment. Two quotations from recent articles agree with our own experience and conclusions. Linksz [1] stated:

> Orthoptics was rendered a poor service by those early enthusiasts who defined it as the nonoperative, as opposed to the operative treatment of squint. There is but one way of treating squint; namely, by the purposeful integration of a number of different procedures, of which surgery, while the most dramatic, is but one, and orthoptics is another.

Lancaster [2] reported:

> Orthoptics is not exercising of the ocular muscles; it is not even primarily a procedure designed to straighten the eyes. It is the teaching of a patient to use his two eyes together for comfortable binocular vision. The emphasis in such training is the teaching of a skill in the use of unskilled neuromuscular coördination. Orthoptics will be of much greater value to physicians and their patients when its function is re-evaluated; not as primarily concerned with anomalies of eye position, but as devoted to helping the patient learn comfortable binocular visual habits.

At first, our efforts in orthoptic therapeutics were directed entirely toward the correction of squint in young persons. We soon discovered that we could not expect improvement in coordination with exercises alone, but that it was necessary to correct refractive errors by glasses and gross deviations by surgical means before much effect from orthoptic training could be expected. In addition, amblyopia must first be combated by occlusion, and in our experience no technic of occlusion other than complete occlusion of the seeing eye over a period of months has ever given satisfactory results. We have many records of cases in which visual acuity in an amblyopic eye has increased from 6/60 to 6/6 and remained so after removal of the occluder. On the other hand, we have had many patients whose vision could not be improved beyond 6/15, although there was no apparent ophthalmoscopic reason for the absence of improvement. Unless visual acuity is improved to 6/12 or better, our experience indicates that the ultimate goal of normal position of the eyes and third degree fusion cannot be reached. An exception to complete occlusion is made in the case of an accommodative squint; in such a case the stripping [3] or lacquering of one lens is often desirable in an effort to overcome suppression.

Outstanding in our records were 2 cases in which use of glasses was not indicated, since orthoptic training accomplished normal coordination of the eyes. The first case was one of convergence excess. H. W., a child aged 4 years, was a patient of Dr. J. B. Blue and Dr. J. B. Stanford, who have given us permission to report their case in detail. The child wore no glasses, no refractive error being found on examination with homatropine cycloplegia. Visual acuity was 6/7.5 in each eye. The patient could hold his eyes parallel for distant vision, but on fixation of any object within a range of 3 feet (90 cm.) his left eye converged about 35 degrees. Fortunately, he was aware of diplopia as soon as his eye turned in, and he would immediately make an effort to straighten it, but it was impossible to focus for near vision. The child was placed under a regimen of daily orthoptic training, and at the end of several months he was able to read, draw, and the like, with the eyes held straight. He has used the stereoscope at home since and will undoubtedly require continued supervised training at intervals for several years longer.

In the second case, that of M. T., a girl aged 4 years, one of us (R. O. R.) had performed a successful operation for alternating convergent squint of 50 prism diopters. Glasses were not worn because the total refractive error determined with atropine cycloplegia was only a + 0.50 D. sphere. Visual acuity was 6/6 in each eye. The eyes

1. Linksz, A.: Objectives of Orthoptic Examination and Treatment, Am. J. Ophth. **26**:552 (May) 1943.

2. Lancaster, J. E.: Orthoptics: Education in Binocular Skill, Am. J. Ophth. **26**:463 (May) 1943.

3. Lyle, K., and Jackson, S.: Practical Orthoptics in the Treatment of Squint, London, H. K. Lewis & Co., Ltd., 1937, p. 33.

remained in perfect position for eight months, when, after a fright during a tornado, there was immediate convergence, with development of convergent squint of nearly the original amount. The patient was then placed under a regimen of daily orthoptic treatments. The condition gradually improved, but she had alternately good and bad days. On bad days the deviation measured 38 prism diopters of esophoria and 2 prism diopters ot left hyperphoria. On good days her eyes were perfectly straight. With regular treatment for a month, she was able to hold her eyes parallel for several days at a time and was sent home with a stereoscope and simple fusion cards. She has been checked at intervals, and for the past year has shown no tendency toward deviation from the normal (fig. 2).

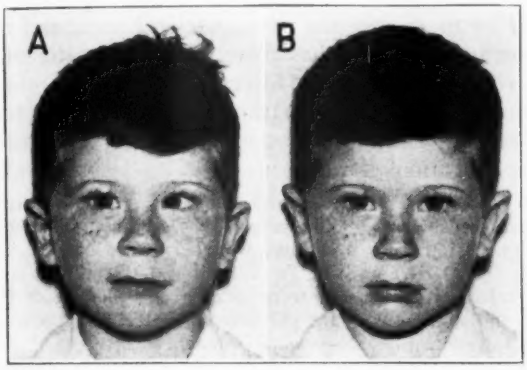

Fig. 1 (H. W.).—*A*, convergence excess prior to orthoptic training; *B*, result of orthoptic training.

ANOMALOUS RETINAL CORRESPONDENCE

Anomalous retinal correspondence, or false projection, is a difficult problem in the rehabilitation of patients with squint and is best handled by the trained orthoptic technician.

In the past five years, 36 per cent of the patients with squint examined in the orthoptic clinic had false projection. This agrees well with the reports of other workers, i. e., Davis,[4] 36 per cent; Pugh,[5] 50 per cent; Travers,[6] 50 to 60 per cent, and Hardy,[7] 60 per cent.

False projection has proved to be one of the greatest stumbling blocks in the training of true binocular coordination. The importance of detection of this condition when the original diagnosis is made cannot be emphasized too strongly. Neglect in taking note of anomalous correspondence amounts to emphasizing, instead of alleviating, the squint. The following cases serve to illustrate this statement:

Case 1.—A. P. had alternating exophoria, with divergence excess. She reported fusion at 10 prism diopters of exophoria, but at this angle on the synoptophore or with correction by prisms there was definite shifting. She appeared to use an eccentric area of her right eye only in binocular vision, the fixation of each eye separately being true. Shifting was eliminated with a prism of 22 D., base in, and true fusion and stereopsis were finally obtained at this angle. If false projection had been ignored, exercises would have been given at the false angle, with the result that the squint would have become permanent. Instead, however, all exercises at first were given at what appeared to be the true angle until fusion was obtained. After fusion was well fixed at the true angle, adduction exercises were carried out, great care being given to observe that the patient did not revert to use of the old false area. When treatment was stopped, she had true fusion and stereopsis and held her eyes straight. Since the condition was divergence excess, much depended on the control she exerted when looking at distant objects.

Case 2.—L. M. reported fusion at zero and at 10 D. of prism, base out. The true angle appeared to be 23 D. of prism, base out. The left eye projected falsely. Treatment was given at the true angle, and the lower half of the lens for the left eye was also occluded to prevent binocular vision for near vision but to encourage it for distant vision. It was not possible to say whether the patch was used correctly, but the results were fairly good. The final result was true fusion at 8 prism diopters of esophoria—the patient could overcome this and use the eyes held straight.

Fig. 2 (M. T.).—*A*, convergent squint prior to operation; *B*, result of operation and orthoptic training.

Case 3.—F. L. reported fusion at 10 D. of prism, base out, but the child had definite exophoria. The true angle seemed to be 10 prism diopters of exophoria. Good fusion and stereopsis were developed at this angle. The eyes were held straight, and good convergence ability was acquired. If the fact that the subjective angle was false had not been taken into consideration, exophoria would have been emphasized, rather than overcome.

Particularly in operative cases we find that an abnormal retinal correspondence which has existed before operation is a handicap in post-

4. Davis, W. T.: Orthoptic Treatment of Strabismus, Tr. Am. Acad. Ophth. **41**:599, 1936.

5. Pugh, M.: Significance of False Projection in Squint, Arch. Ophth. **12**:459 (Sept.) 1934.

6. Travers, T. a'B.: Comparison Between the Visual Results Obtained by Various Methods Employed for the Treatment of Concomitant Strabismus, London, George Pulman & Sons, Ltd., 1936.

7. Hardy, L. H.: Orthoptics, Graduate Lecture read at the meeting of the American Academy of Ophthalmology, 1938.

operative treatment. The patient has a tendency to want to revert to his old habit, and much valuable time is lost at this strategic moment—immediately after operation. Theoretically and ideally, the most advisable procedure seems to be occlusion for development of macular fixation of the squinting eye and then operation, followed by treatment. This, for various reasons, is not possible in all cases.

We have the record of a patient (P. B.) whose case demonstrates what a handicap abnormal correspondence can be in postoperative training. He was an out-of-town patient and had been given no preoperative treatment. Immediately after operation he reported fusion on the synoptophore at 0 and 3 D. of prism base in. At this angle shifting was seen, and it appeared that his true angle was more nearly 10 D. of prism base out. He returned to his home within a few days, and there was no opportunity to give him any kind of binocular training. If this had been possible, however, treatment would have had to be given at his objective angle, in an attempt to develop true fusion. At this time, if it had not been for the falsely used area, abduction exercises would have been indicated. The outcome in a case of this kind is often a cosmetic, rather than a functional, improvement.

DIVERGENCE EXCESS

It is not possible to make a general statement concerning patients with divergence excess, since so much depends on the person. The tendency to diverge to excess for distance usually remains, but development of the ability to overcome this tendency is the purpose of orthoptic training. The factors of cooperation and mental effort on the part of the patient affect to a great extent the final result. Many such patients require operation, as well as orthoptic training.

The factor of mental effort is one which cannot be ignored in the successful treatment of any kind of binocular imbalance. Without the patient's full cooperation, and that cooperation includes a positive striving toward the goal as explained by the physician and kept in view by the technician, the achievement of the desired result will be hindered. This is true with patients of all ages.

The adult, who as a rule seeks relief from discomfort, should give his cooperation without question. Yet surprisingly often he has to be persuaded to do so. We believe the best method with adults is the full explanation of the common sense basis of the treatment. The sound logic of orthoptic training, coupled with its comparative ease and simplicity, should appeal to the average intelligent adult.

In the case of the teen age patient the cosmetic result is usually the point of attraction. With the small child the idea of showing what he can do seems to be the theme to stress. Some entertainment is necessary, and the child with imagination is the ideal patient. The method of reward, however wrong psychologically, must at times be resorted to. Much ground is gained when the person working with the child can secure his affection and esteem. It should be stressed that securing of this cooperation, by whatever means, is all-important with patients of all ages.

In our cases of retinal detachment, we have with impunity severed extraocular muscles in order to expose the proper scleral area, and in but few instances has there been any postoperative heterophoria. However, the report of a single case will illustrate the aid which the orthoptic clinic can give in the treatment of such complications.

A. D. M., a man aged 65, sustained an enormous tear and detachment of the retina in December 1937, for which diathermy operation was performed by one of us (R. O. R.) on Jan. 7, 1938. The left superior and external rectus muscles were reflected and then resutured to the stumps with fine chromic catgut. After recovery of normal vision, there were pronounced divergence and hypertropia of the left eye. On the synoptophore there were simultaneous macular perception, fusion and stereopsis at 24 D. of prism, base in, and left hypertropia of 7 to 18 prism diopters. Diplopia and vertigo were constant symptoms. Thirteen orthoptic treatments resulted in notable improvement in ocular measurements to 10 D. of prism, base in, with hyperphoria of 6 prism diopters. The patient later overcame this defect by constant effort and obtained fusion and stereopsis at zero. He has maintained this ability up to the present, with entire relief from his symptoms.

DIVERGENCE INSUFFICIENCY

Many patients with divergence insufficiency are made more comfortable when the power of prism divergence is built up. The clinic records the experience of many men who failed the preliminary Army aviation tests because of weakness in divergence power but who were enabled through proper exercises to qualify for the Air Forces. Similar results were experienced by laboratory technicians who had difficulty in the use of the binocular microscope and by patients with headaches and other symptoms of asthenopia for which no cause other than mild heterophoria could be discovered and who became perfectly comfortable after orthoptic training.

CONVERGENCE INSUFFICIENCY

In our experience the patients who have the best prognosis and respond most rapidly are those with convergence insufficiency. Treatment for alleviation of this condition is admittedly simple, but it does not follow that this deficiency is any less worthy of notice. Patients suffering

from lack of good convergence ability feel real discomfort which, though not disfiguring or serious, can hamper them considerably in their work. Sometimes the symptoms are experienced only with close work, whereas, again, discomfort is felt rather generally with use of the eyes at any distance. Training of a better and easier convergence habit at the office, supplemented by home exercise, is the usual procedure. Many out-of-town patients with this condition are seen. Happily for them, successful treatment can be directed at home. Of course, as is the case in any kind of training process, much depends on the amount of effort put forth by the patient. It is true, however, that more can be done for himself by a patient needing exercises for convergence insufficiency than can be done by a patient with any other condition. It is probable that there are physicians who disparage treatment for convergence insufficiency, dismissing the sufferer with a half-hearted suggestion concerning finger to nose convergence exercises. There are also persons with convergence weakness who are advised simply not to use their eyes for much close work, and who inevitably become dissatisfied patients. We feel it urgent to bring these possibilities to mind, since in our experience many patients with this condition, who are uncomfortable, although they have had proper refraction, are completely relieved by orthoptic training.

TRUE AND LATENT CONVERGENCE INSUFFICIENCY

In this field, we should like to differentiate between true convergence insufficiency, in which the diagnosis is apparent because of a marked recession of the convergence near point, a high degree of exophoria for near vision or a frank disparagement in the normal 3:1 or 4:1 relation of prism convergence to prism divergence, as measured on the phorometer, and a latent or hidden tendency to convergence insufficiency, as demonstrated by normal phorometric measurements accompanied by a history of ocular discomfort on close use of the eyes. The latter we believe to be the condition of a large group of patients who make the rounds of various ophthalmologists and who are usually thought to be victims of neurasthenia or hysteria. Careful checking with the phorometer may disclose a slight weakness in prism convergence, but usually the measurements of the muscle strength are within normal limits. However, examination with the junior metronoscope, equipped with rotary prisms, will invariably disclose a poor reading ratio, i. e., the relation of prism convergence to prism divergence, which should be at least 2:1, and preferably 3:1 or 4:1. On this instrument are simulated the fixations and regressions which are a part of the normal reading habit. Measurements of the vergences under the stress of movement of the eyes from left to right, as in reading, give a true estimate of muscle power in ocular activity, as compared with the static measurement of unmoving eyes examined on the phorometer by fixation of a single point object. Since acquainting ourselves with the value of prism reading tests for such patients, we have looked more closely for the latent convergence insufficiencies and find that they occur more frequently in our practice than we would have believed possible.

The diagnosis of convergence insufficiency is often easy—the existence of a condition of greater exophoria for near than for distant vision, together with a poor convergence near point. However, there is no definite rule which can be set up concerning exact measurements that leads to a diagnosis of this difficulty. First, symptoms vary greatly—from headaches, double vision, tired eyes and burning lids to dizziness and actual unsteadiness in walking. We have found many combinations of symptoms, as well as many different groupings of indicative measurements. There sometimes exists a decided exophoria for near vision with a good convergence near point. At other times there may be a poor convergence near point with a normal physiologic exophoria. Either of these combinations of measurements may be present with good or poor prism vergences.

There is, however, a significant finding that in our experience consistently indicates the need for convergence training at the near point. This measurement is called the reading ratio. It is the ratio of prism divergence to prism convergence at the near point during actual reading, which involves the changing of fixation, as is done normally during reading or during use of the eyes in almost any other occupation. In a few instances this measurement has been the only indication of the difficulty present. In other cases it has been a deciding factor in the course of treatment. In all cases it has borne out the testimony of other positive diagnostic measurements.

There may be several ways of setting up means of taking a reading ratio, but the method we have found most satisfactory is the use of a table model of the junior metronoscope. This is an instrument equipped with reading rolls lighted from within and with an automatic shutter arrangement whereby fixation is necessarily changed in order to read the complete line. There is also firmly attached a set of rotary prisms at reading distance, complete with head rest. The patient places his head firmly against the rest

with his eyes close to the prisms. The reading correction is worn. As the prisms are turned base in and base out to find the breaking point, the patient changes his fixation as he reads across the line, guided by the opening and closing of the shutters. The resulting ratio is one prism of divergence to prism convergence—a relation made more significant in the case of convergence insufficiency, since the patient is actually doing the thing with which he has trouble while the measurement is being made. We find the same relation between prism divergence and prism convergence is necessary for comfort in reading as for distance vision.

It can easily be seen that by means of the same instrument, the metronoscope, the training of better convergence can be effectively given and the diagnosis of convergence deficiency made. We depend to a great extent on this instrument for the treatment of persons with this weakness. Other methods include the use of the synoptophore, the stero-orthopter and the Remy separator.

In the past five years the clinic has had 453 patients with convergence insufficiency, 148 of whom, or 33 per cent, would be classified as having latent convergence insufficiency. Of 136 patients with convergence insufficiency treated in the clinic, 52, or 38 per cent, would be said to have the latent form. Of the 136 patients treated, 125 felt their trouble was definitely improved. Of the 11 for whom no improvement was recorded, 5 dropped out and did not complete the treatment. The remaining 6 patients had other conditions, such as allergy and migraine, which were partly responsible for the symptoms for which they sought relief.

Ninety-one persons with convergence insufficiency were given home treatment, consisting mainly of the use of a stereoscope and delta "base out" cards. Simple fusion cards made at the office were given children for home use. Other training included the use of loose prisms base out, finger to nose convergence exercises and voluntary convergence exercises[8] with finger and distant object. (The subject fixes on the finger at a near point, being conscious of a double distant object; the finger is then removed, and the patient tries to keep the image of the distant object doubled by looking at an imaginary near point.)

CONCLUSION

We have found the Memphis Orthoptic Clinic a valuable adjunct in the handling of our private patients, and we expect to profit by its continued aid in the future.

1720 Exchange Building.
1720 Exchange Building.
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8. Lyle and Jackson,[3] p. 153.

DRUSEN OF THE OPTIC NERVE SIMULATING CEREBRAL TUMOR

NATHAN S. SCHLEZINGER, M.D.; JOSEPH WALDMAN, M.D., AND BERNARD J. ALPERS, M.D.

PHILADELPHIA

Drusen of the optic nerve constitute a characteristic ophthalmologic disorder, which was first described in 1858 by Müller.[1] In addition to the term drusen, the same condition has been referred to by various authors as "hyaline bodies," *Drusenbildungen* and *Kalkdrusen*. A review of the literature discloses that the occurrence of drusen of the optic nerve without symptoms is well known. Some authors have pointed out the association of drusen of the optic nerve with ophthalmologic diseases, such as retinitis pigmentosa, glaucoma and melanosarcoma. Several have noted the relatively frequent concurrence of drusen of the optic nerve with disorders of the nervous system.

Our attention was recently directed to this interesting neuro-ophthalmologic disorder by the observation of 2 patients who demonstrated that drusen of the optic nerve may in some instances be characterized by clinical features closely resembling those of tumor of the brain. Although pneumoencephalographic study may be necessary in order to establish definitely the correct diagnosis, we wish to call attention to cases of this type because the outlook and management are so different from the prognosis and treatment of tumors of the brain.

REPORT OF CASES

CASE 1.—*Right hemicrania for years; left-sided headaches for three years. Drusen of the optic nerve, with slight elevation of the disk. Results of neurologic examination negative; pneumoencephalogram negative for cerebral tumor.*

History.—J. M., a woman aged 23, a woolen mill worker, was admitted to the neurologic service of the Jefferson Medical School Hospital on March 19, 1940, complaining of headache for three years. Her father had been subject to convulsive seizures, and the mother had migraine; the family history was otherwise without interest from a neurologic standpoint. The past history revealed the occurrence of typical hemicrania as long as the patient could remember, the free interval between headaches varying from four to six weeks. The headaches were on the right side; they usually appeared prior to the menstrual period, were characterized by prodromal paresthesias involving the face, tongue and arm homolaterally and were associated with vomiting and with amblyopia involving the right eye. Except for the typical attacks of migraine, the patient had been in good health until about three years before admission to the hospital, when the right hemicrania was gradually replaced by headaches in the left parieto-occipital region, associated with pain in the left eye. These headaches were relieved temporarily by the wearing of glasses, but they soon recurred and became progressively more frequent and more intense. In the months preceding admission the headache was present daily and often awoke the patient during the night. Tinnitus and transient vertigo were noted for several weeks preceding admission. There were no other symptoms referable to the nervous system.

Physical Examination.—The patient was well developed. A scar on the right side of the neck was the result of removal of a cyst ten years before. The heart, lungs and abdomen were grossly normal. The blood pressure was 120 systolic and 70 diastolic.

Neurologic Examination.—Station and gait were normal. There was a fine tremor of the eyelids and of the fingers on extension. No evidence of ataxia or incoordination was noted. The motor power was well preserved everywhere. The tendon reflexes were equal and active everywhere except for a relatively hyperactive patellar reflex on the left side. The abdominal reflexes were active and equal on the two sides. There were no pathologic reflexes. Pain, position and vibration senses were intact. There was slight facial asymmetry but no true weakness of the face, palate or tongue. Neuro-ophthalmologic examination showed relative prominence of the right eye, verified by the exophthalmometer (right eye, 22 mm. and left eye, 15 mm.). The pupils were round, regular and equal and reacted well to light and in accommodation. The extraocular movements were normal. The corneal reflexes were equally active on the two sides. Examination of the fundus disclosed many lemon yellow drusen on and near the upper and nasal margins of the optic disk bilaterally. The borders of the nerve head elsewhere were free of drusen and appeared striated and somewhat gray. The optic disks appeared elevated, but the degree of elevation could not be measured. The physiologic cup was present but small. The ratio of vessels was normal. The macular area was normal.

Laboratory Studies.—The results of urinalysis and the blood count were within normal limits. The sugar of the blood measured 91 mg. and the nonprotein nitrogen 39 mg. per hundred cubic centimeters. The Wassermann reactions of the blood and the spinal fluid were negative. The cerebrospinal fluid showed an initial pressure of 165 mm., contained less than 1 cell per cubic millimeter and had a total protein content of 12 mg. per hundred cubic centimeters. The electrocardiogram was normal. The basal metabolic rate was + 1 per cent. Roentgenographic examination of the skull, including special views of the sella turcica, the orbits and the

From the Department of Neurology, Jefferson Medical College of Philadelphia.

Read at a meeting of the College of Physicians of Philadelphia, Section on Ophthalmology, Oct. 21, 1943.

1. Müller, H.: Anatomische Beiträge zur Ophthalmologie, Arch. f. Ophth. **4** (pt. 2):1, 1858.

optic foramens, revealed nothing abnormal. An encephalographic study on March 26 showed a well outlined ventricular system, which was symmetric and showed no displacement or filling defects (fig. 1).

CASE 2.—*Frontal headaches for one and a half years; nausea and vomiting. Drusen of optic nerves, with 1 to 1.5 D. of papilledema bilaterally; constriction of visual fields and enlargement of blindspots. Results of neurologic examination negative; pneumoencephalogram negative for cerebral tumor.*

Fig. 1 (case 1).—Encephalogram, showing a symmetric ventricular system, with no displacement or filling defects.

History.—F. C., a motorman aged 35, was admitted to the neurologic service of the Jefferson Hospital on Jan. 28, 1942, complaining of headaches for the past one and a half years and of vomiting for the past two years. One brother had committed suicide; the mother, the sister and a nephew were known to have had cystic nodules over various parts of the body; the family history was otherwise without significance from a neurologic standpoint. The past history included a tonsillectomy at 10 years of age and an appendectomy at 20 years of age. While he was working in a coal mine, at the age of 17, the patient sustained an injury to his left leg, which was not severe. Cystic nodules had been removed from behind the left ear and the left elbow. Except for these episodes the patient had apparently been in good health until the onset of his present difficulty, which developed gradually early in 1940.

At this time vomiting began, as often as two or three times a day, usually, but not always, accompanied by nausea. During the summer of 1940 frontal headaches appeared, dull in character and lasting three or four hours. These attacks occurred three or four times a week at first, but they became more intense and more frequent until they were almost constant by the summer of 1941. The vomiting persisted unchanged until November 1941, but after this it was observed on only four or five occasions. The headaches occurred without change until his admission to the hospital. The patient had noted increased fatigability and some unsteadiness of gait at times prior to entrance.

Physical Examination.—The patient was fairly well developed. There was evidence of pronounced lymphoid hyperplasia in the pharynx. The heart, lungs and abdomen were grossly normal. The blood pressure was 120 systolic and 80 diastolic. There was a post-traumatic scar on the left leg.

Neurologic Examination.—Station and gait were within normal limits. There was no evidence of ataxia or incoordination. The tendon reflexes were equal and active except for an inconstant, relatively hyperactive biceps reflex on the left side. The abdominal reflexes were active. The plantar reflex was not pathologic. Pain, position and vibration senses were intact. The pupils were round, regular and equal and reacted well to light and in accommodation. The extraocular movements were normal. The corneal reflexes were active. There was no weakness of the face, palate or tongue. Neuro-ophthalmologic examination showed the following abnormalities in the fundus bilaterally (fig. 2): The temporal and superior portions of the optic disk had a dirty gray pallor; the cup was small, and the lamina cribrosa was not seen. Characteristic drusen, lemon yellow in color, were scattered throughout the nerve tissue of the optic disk. The superior and nasal margins of the optic disk were indistinct and elevated to a level between 1 and 1.5 D. The appearance of the retinal vessels was normal, and there were no retinal exudates or hemorrhages. Visual acuity without correction was 20/20 in the right eye and 20/30 in the left eye. Examination of the visual fields (fig. 3) showed slight peripheral constriction and slight enlargement of the blindspot bilaterally.

Laboratory Studies.—The blood count and the results of urinalysis were within normal limits. The sugar of the blood measured 79 mg. and the nonprotein nitrogen 30 mg. per hundred cubic centimeters. The Wassermann reactions of the blood and the spinal fluid were negative. The cerebrospinal fluid had an initial pressure of 170 mm., contained less than 1 cell per cubic millimeter and had a total protein content of 24 mg. per hundred cubic centimeters and a normal colloidal gold curve. Laryngologic examination and biopsy of tissues from the nasopharynx confirmed the clinical impression of marked lymphoid hyperplasia of the pharynx. Roentgenographic examination of the skull, including special

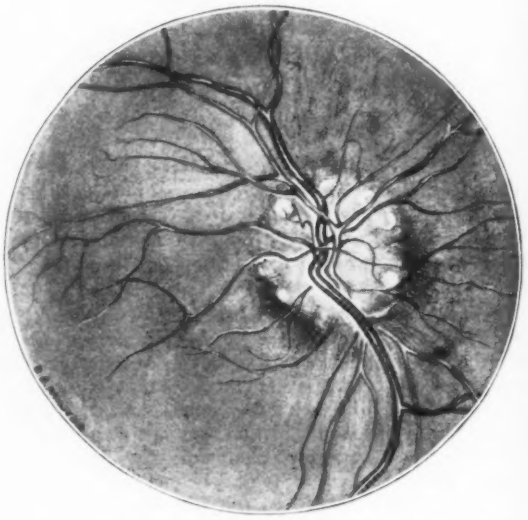

Fig. 2 (case 2).—Fundus of the right eye, showing characteristic drusen and an indistinctly outlined optic disk, with measurable elevation.

views of the base and sinuses, revealed nothing abnormal. An audiometric test showed no significant impairment of hearing. The Bárány test revealed changes suggestive of multiple lesions involving the brain stem, together with absence of shock reaction. An electroencephalogram revealed normal cerebral potentials except for showers of sharp and slow wave formations in

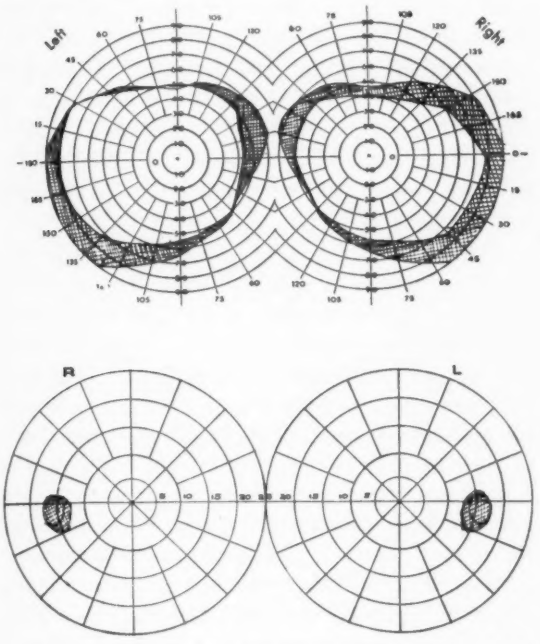

Fig. 3 (case 2).—Visual fields, showing slight peripheral constriction and slight enlargement of the blindspot bilaterally.

the left frontal and parietal areas, the significance of which was doubtful. Encephalographic examination, performed on February 7, disclosed (fig. 4) that the ventricles were well filled with air and were symmetric and normal in size and shape. The third and fourth ventricles were well shown and appeared normal. There was air in the basal cisterns and in the subarachnoid pathways.

After this procedure, the symptoms present on admission disappeared, and at the time of discharge the patient was asymptomatic.

The anamnestic data in these cases reveal a clinical syndrome chiefly characterized by headache, vomiting and an altered appearance of the optic disks somewhat suggestive of early papilledema. Therefore it is not surprising that the diagnostic possibility of cerebral tumor was seriously considered in both cases. This was true in spite of the fact that the drusen were detected in the optic nerves by the neurologist and the ophthalmologist. The conspicuous headache and vomiting, as well as such minor symptoms as vertigo, were believed to be sufficient to warrant an intensive search for the presence of cerebral tumor.

In case 1 the possibility of a close relation between the existing headaches and the past history of typical migraine was not overlooked. But such a relation was rejected because the patient's recent headaches differed so considerably from her previous migraine headaches. In case 2 there was no past history of headaches; the patient showed definitely measurable elevation of the optic disks, a slight peripheral constriction of the visual fields and enlargement of the blindspots.

No evidence of increased intracranial pressure was demonstrable by lumbar puncture in these cases. Routine chemical examination of the spinal fluid showed no abnormalities. Pneumoencephalographic studies in both cases disclosed no evidence of tumor of the brain, and the results were considered to be within normal limits. The results of our study in these 2 cases made evident the fact that the symptoms were not due to tumor of the brain. This conclusion directed our attention to the problem of correlating with drusen of the optic nerve the clinical syndrome which commonly is associated with cerebral tumor.

In 2 cases reported by Reese [2] the symptoms and signs were strikingly similar to those observed in our cases, and the presence of tumor of the brain was similarly suspected. In this connection it is interesting to observe that in both our cases there was a history of removal of cystic masses from the various parts of the body and that in case 2 there was a history of similar cysts affecting several persons of the same family. This may tend to support the

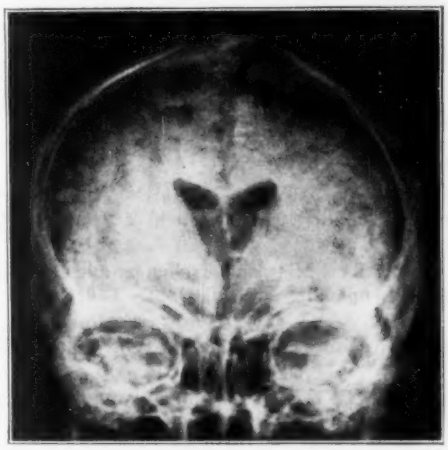

Fig. 4 (case 2).—Normal encephalogram.

hypothesis offered by Reese [2] in which drusen are considered to be *formes frustes* of tuberous sclerosis. The latter condition, in turn, was classified with conditions such as multiple neuro-

2. Reese, A. B.: Relation of Drusen of the Optic Nerve to Tuberous Sclerosis, Arch. Ophth. **24**:187 (July) 1940.

fibromatosis, Hippel-Lindau disease and the Sturge-Weber syndrome by van der Hoeve,[3] who suggested the term "phakomatoses" for all.

COMMENT

In order to evaluate the clinical significance of drusen of the optic nerve, this neuro-ophthalmologic disorder should be considered from a variety of standpoints. Since the time of the first report by Müller,[1] various suggestions as to the cause and pathogenesis of this condition have been offered. Predisposition was the etiologic factor favored in the report of Ancke,[4] Lauber,[5] Braun[6] and Leimgruber,[7] in which familial incidence was a conspicuous feature. Advanced age as an etiologic factor was suggested by Terson[8] but was disproved by Walker's[9] report of drusen in a 9 year old boy and by Gifford's[10] case of the lesion in an 11 year old girl. The age of onset is obscure in all cases, since the drusen are discovered incidentally in examination of the fundus. Sex was demonstrated to be an unimportant factor in the series reported on by Höeg,[11] in which 30 patients were females and 23 males. Toxic or infectious etiologic factors are conspicuously absent in the vast majority of cases; Lauber[5] reported a case in a man with alcohol-tobacco amblyopia. Cirincione[12] showed that drusen of the optic nerve do not have the same origin as drusen of the choroid. Iwanoff[13] expressed the belief that drusen were colloid bodies. Oeller[14] disagreed with this concept and suggested that drusen originated as droplets of myelin. Coats[15] favored the origin from "small homogeneous droplets of hyalin." Lauber stated that misplaced pigment epithelium was the probable site of origin. Parsons[16] offered the theory of origin from antecedent exudates in the nerve head. Fuchs[17] favored the origin from neuroglia, and this theory was also supported by Collins and Mayou.[18] Corrado[19] postulated that the source of drusen was in the nature of "heterotopic calcinoses," due to parathyroid dysfunction. Reese[2] offered the hypothesis that drusen are *formes frustes* of tuberous sclerosis.

The preponderance of evidence supports the belief expressed by Fuchs[17] that drusen are derived from the neuroglia cells in the optic nerve, probably as a result of some local irritative process, although either metabolic or degenerative processes are possible. Therefore, whatever the ultimate origin, it is likely that drusen start as minute globules of hyalin, which increase in size by accretions in layers or by fusion. Hyalin deposits in the neuroglia were observed by Goldstein and Givner.[20] Tobler,[21] in a comprehensive treatise, described the results of a series of chemical analyses. He concluded that drusen were composed of a split product of albumin which is similar to hyalin, and which has a tendency to take up calcium.

Samuels[22] strongly favored Fuchs's hypothesis that drusen arise from abnormal secretions of hyalin by proliferative neuroglia cells in the papilla. Hirschberg and Cirincione[23] proved that

3. van der Hoeve, J.: Eye Symptoms in Phakomatoses, Tr. Ophth. Soc. U. Kingdom **52**:389, 1932.

4. Ancke, R.: Beiträge zur Kenntnis von der Retinitis pigmentosa, Centralbl. f. prakt. Augenh. **9**:167, 1885.

5. Lauber, H.: Klinische und anatomische Untersuchungen über Drusen im Sehnervenkopf, Arch. f. Ophth. **105**:567, 1921.

6. Braun, W.: Ueber familiäres Vorkommen von Drusen der Papille, Klin. Monatsbl. f. Augenh. **94**:734, 1935.

7. Leimgruber, M.: Erbforschungen über die Drusen der Sehnervenpapille, Arch. f. Ophth. **136**:364, 1936.

8. Terson, A.: Les verrucosités hyalines de la portion papillaire du nerf optique, Arch. d'opht. **12**:367, 1892.

9. Walker, C. H.: A Case of Hyaline Bodies at the Optic Disk, Tr. Ophth. Soc. U. Kingdom **35**:366, 1915.

10. Gifford, H.: An Unusual Case of Hyaline Bodies in the Optic Nerve, Arch. Ophth. **24**:395, 1895.

11. Höeg, N.: Ueber Drusen im Sehnervenkopf, Arch. f. Ophth. **69**:355, 1908.

12. Cirincione, C.: Concrezioni nella testa del nervo ottico, Clin. ocul. **5**:1599, 1904.

13. Iwanoff, A.: Ueber Neuritis optica, Klin. Monatsbl. f. Augenh. **6**:421, 1868.

14. Oeller, J. N.: Beiträge zur Lehre von der Chorioretinitis pigmentosa, Arch. f. Augenh. **8**:435, 1879.

15. Coats, G.: Concretions in the Papilla and Corpora Amylacea in the Retina, Tr. Ophth. Soc. U. Kingdom **32**:119, 1912.

16. Parsons, J. H.: Hyaline Bodies at the Optic Disc, Tr. Ophth. Soc. U. Kingdom **23**:136, 1903.

17. Fuchs, A.: Atlas der Histopathologie des Auges, Vienna, Franz Deuticke, 1927.

18. Collins, E. T., and Mayou, M. S.: Pathology and Bacteriology of the Eye, ed. 2, Philadelphia, P. Blakiston's Sons & Co., 1925.

19. Corrado, M.: Sulla patogenesi della concrezioni calcarie della papilla in rapporto ai processi di calcinosi, Ann. di ottal. e clin. ocul. **62**:721, 1934.

20. Goldstein, I., and Givner, I.: Calcified Hyaline Deposits (Drusen) in the Optic Disk, Arch. Ophth. **10**:76 (July) 1933.

21. Tobler, T.: Ueber Kalkdrusen in der Papille des Nervus opticus und über Kombination derselben mit zystoider Entartung der Macula lutea, Ztschr. f. Augenh. **47**:215, 1922.

22. Samuels, B.: Drusen of the Optic Papilla, Arch. Ophth. **25**:412 (March) 1941.

23. Hirschberg, J., and Cirincione, G.: Ueber Drusen im Sehnervenkopf, Zentralbl. f. prakt. Augenh. **15**:166, 1891.

drusen were not amyloid in composition, and they described the evolution of a gas when the hyalin bodies were treated with hydrochloric acid.

Clinicopathologic descriptions have been made by Hirschberg and Cirincione,[23] Gurwitsch,[24] de Schweinitz,[25] Sachsalber,[26] Cirincione,[12] Coats[15] and Lauber.[5] In two recent reports by Reese[2] and Samuels,[22] the results of careful pathologic study of eyes containing drusen of the optic nerve have been recorded. Reese[2] stated that the incidence of drusen over a 7 year period in routine microscopic examinations of eyes removed for various causes was 1 per cent of a series of 893 globes. Histopathologic study of eyes containing drusen of the optic nerve discloses that the lesions are usually situated on the nasal side and, with rare exceptions, anterior to the lamina cribrosa. According to Samuels,[22] an especially frequent location for drusen is on the nasal side, in the recess between the scleral spur and the lamina cribrosa. The lesions consist of a variable number of discrete nodules or of a conglomeration of partially fused nodular masses, which have a concentrically laminated structure. A large conglomerate mass is characteristically associated with smaller satellite lesions. The bulb of the lesion is composed of an amorphous, hyalin substance, which not infrequently shows evidence of calcification. These nodular masses are not encapsulated and thus differ definitely from corpora amylacea; the latter also are distinguished by the fact that they show no lamellation. Drusen are differentiated from corpora aranacea by the fact that the latter are always situated behind the lamina cribrosa, are usually calcified and are closely related to the dura or the arachnoid.

In the earliest stage of development drusen of the optic nerve appear as pale yellow, glistening points in the optic disk, usually near the edges. It is at this stage that the diagnosis is uncertain, especially when there is a coexisting ocular ailment. The nasal side of the papilla seems to be the area most frequently affected. This side is also the site of predilection for glial membranes, which is in keeping with the fact that the papilla is thicker on the nasal side, with, consequently, more glial tissue present there. In the later stages of development, the diagnosis becomes more certain as the drusen assume their more typical appearance in the form of round, discretely grouped or conglomerate, partially fused nodular masses, which are gray-white or blue-white. The drusen tend to become increasingly massed near the edge of the disk, although they are sometimes scattered throughout.

The appearance of drusen on examination of the fundus varies with the depth of the lesion. The drusen which are situated anterior to the choroidal ring are easily recognizable and present a striking ophthalmoscopic picture. They may reflect the light with much brilliance, appearing as shining white or pale lemon yellow bodies, with beadlike contour. They have been described in picturesque terms as resembling a shower of gold coins, a cluster of grapes, a mass of frog eggs or tapioca grains. They are more or less translucent. As a lobulated mass they may completely cover the optic disk, which may be swollen. An increase in elevation as high as 14 D. has been reported. In addition to the possible elevation, there may be an increase in diameter of the papilla, due to extension into the surrounding retina. The drusen may be either anterior or posterior to the retinal blood vessels, and occasionally a mass of these bodies may completely hide the vessels at some point in their course. It is doubtful whether calcification of the lesion can be distinguished by means of the ophthalmoscope.

The drusen which are situated deep in the sclerochoroidal canal are probably not visualized with the ophthalmoscope because of the overlying cover of nerve fibers and capillaries. These drusen are especially important to bear in mind clinically, since they may produce an abnormal fulness of the papilla, which may be accompanied by enlargement of the blindspot. In many instances, so-called pseudoneuritis may really represent unsuspected, deeply situated drusen. In such cases the possible confusion with early papilledema is obvious.

In most cases observation of the condition over a considerable period shows little or no change in the ophthalmoscopic appearance which would indicate progression. However, in his report of a case of a 9 year old boy, Walker[9] described a progressive increase in the size and number of drusen over a period of four years. Lauber,[5] similarly, observed, in the case of a woman, a notable increase in drusen over a period of fifteen years. Reese[2] also noted growth over a period of two years in a 17 year old youth.

The occurrence of drusen of the optic nerve in association with a variety of local ocular disorders has been described by many authors. The concurrence with retinitis pigmentosa was noted by Müller,[1] Nieden,[27] Oeller,[14] Tillé and Tran-

24. Gurwitsch, M.: Ueber hyaline Bildungen im Sehnervenkopfe und in der Netzhaut bei Morbus Brightii, Zentralbl. f. prakt. Augenh. **15**:225, 1891.

25. de Schweinitz, G. E.: Hyaline Bodies (Drusen) in the Nervehead, Tr. Am. Ophth. Soc. **6**:349, 1892.

26. Sachsalber, A.: Beitrag zur Drusenbildung im Sehnervenkopfe, Beitr. z. Augenh. **3**:1, 1898.

27. Nieden, A.: Ueber Drusenbildung in und um den Optikus, Arch. f. Augenh. **20**:72, 1889.

tas,[28] McKenzie,[29] Remak,[30] Ancke,[4] Morton and Parsons,[31] Walker,[9] Topolanski[32] and Masselon.[33] The coexistence of drusen with melanotic sarcoma was observed by Coats[15] and Cibis.[34] Drusen in conjunction with chorioretinitis was reported by Chevallereau,[35] Juler,[36] Lawson[37] and Löhlein.[38] The association with glaucoma was recorded by Demaria,[39] Athens[40] and Samuels.[22]

Various neurologic disorders have been observed in conjunction with drusen of the optic nerve. Facial nerve paralysis was noted by Hirschberg and Cirincione,[23] and death due to cerebral hemorrhage, by Hirschberg and Birnbacher.[41] Chronic hydrocephalus caused death in the case reported by Wedl and Bock.[42] Hypophysial tumors were present in cases reported by Lauber[5] and Rath.[43] Nieden[44] described 2 cases in which there had been a history of head injury, while de Schweinitz[25] noted that his patient had been shot in the head. Fejér[45] reported on a patient with bilateral paresis of the oculomotor nerve who was also suspected of having tumor of the brain. Meningomyelitis and optic neuritis occurred in a case described by Stood.[46] Neurasthenia was a noteworthy feature in patients reported by Nieden[27] and Coats.[15] Amaurosis and insanity were observed in 1 case by Iwanoff.[13] Mendel[47] noted hysteria and chlorosis in his patient.

In the vast majority of cases of drusen of the optic nerve there is no impairment of vision. Asymptomatic cases with negative anamneses have been described by Nieden,[27] Lauber[5] and Höeg.[11] It is amazing in some instances to note the disproportionately mild effect on vision of what is so often an apparently massive change in the optic disk. This is explained by the histopathologic observation that the optic nerve fibers may be twisted in their course by the drusen but remain normal in caliber. However, there appears to be no doubt that drusen of the optic nerve, in a relatively few cases, may lead to severe impairment of vision. Such cases have been reported by Iwanoff,[13] de Schweinitz,[25] Cirincione,[12] Fejér,[45] Wedl and Bock,[42] Lauber,[5] Rabitsch[48] and Shumway.[49] A patient was observed by Nieden[27] over a period of years, during which exacerbations and remissions in visual impairment were directly correlated with the phasic manner of growth of the drusen. These more serious effects of drusen are probably a result of compression of the optic nerve fibers in the instances in which the drusen are situated in the sclerochoroidal canal.

The usually mild alterations in the visual fields, such as slight enlargement of the blindspot with or without nonspecific peripheral constriction, are directly attributable to the presence of drusen when a coexisting ocular condition has been excluded. Contraction of the visual fields has been reported in such cases by Stood,[46] Nieden,[27] de Schweinitz,[25] Streiff,[50] Rabitsch,[48] Lauber,[5]

28. Tillé, H., and Trantas, N.: Verrucosités hyalines, prépapillaires (drussen) chez un homme jeune atteint de rétinite pigmentaire, Bull. Soc. d'opht. de Paris, April 1934, p. 243.

29. McKenzie, G. W.: Drusen of the Optic Nerve, Retinitis Pigmentosa, and Vitreous Opacities, Eye, Ear, Nose & Throat Monthly **13**:293, 1934.

30. Remak: Ein Fall von excessiver Drusenbildung in der Papille bei atypischer Retinitis pigmentosa, Zentralbl. f. prakt. Augenh. **9**:257, 1885.

31. Morton, A. S., and Parsons, J. H.: Hyaline Bodies (Drusenbildung) at the Optic Disc, Tr. Ophth. Soc. U. Kingdom **23**:135, 1903.

32. Topolanski, A.: Drusen am Sehnerveneintritt und Pigmentdegeneration der Retina, Ztschr. f. Augenh. **20**:584, 1908.

33. Masselon, J.: Infiltration vitréuse de la retine et de la papille, Bull. et mém. Soc. franç. d'opht. **2**:1, 1884.

34. Cibis, P.: Zur Klinik und Anatomie der Drusenbildung in der Papille und über Kombination derselben mit einem Melanosarkom der Aderhaut, Klin. Monatsbl. f. Augenh. **105**:78, 1940.

35. Chevallereau, M.: Verrucosités hyalines du nerf optique et de la choroide, Rec. d'opht. **31**:103, 1909.

36. Juler, F. A.: Hyaline Bodies at the Optic Disc, Tr. Ophth. Soc. U. Kingdom **34**:177, 1914.

37. Lawson, G.: Syphilitic Choroido-Retinitis with Peculiar Growths at the Fundus, Tr. Ophth. Soc. U. Kingdom **3**:117, 1883.

38. Löhlein, W.: Ueber die kegelförmige Papille mit Drusenbildung, Klin. Monatsbl. f. Augenh. **86**:433, 1931.

39. Demaria, B.: Zur Pathogenese der Amotio chorioideae nach Iridektomie bei Glaukom und über Corpora amylacea in der exkavierten Papille, Klin. Monatsbl. f. Augenh. **42**:339, 1904.

40. Athens, A. G.: Glaucoma Associated with Hyaline Bodies (Drusen) of the Optic Disc, Am. J. Ophth. **24**: 1138, 1941.

41. Hirschberg, J., and Birnbacher, A.: Beiträge zur Pathologie des Sehorgans, Zentralbl. f. prakt. Augenh. **9**:65, 1885.

42. Wedl, C., and Bock, E.: Pathologische Anatomie des Auges, Vienna, C. Gerold's Sohn, 1886.

43. Rath, W.: Geschwülste der Hypophysis cerebri, Arch. f. Ophth. **34**:81, 1888.

44. Nieden, A.: Drusenbildung des Optikus, Ztschr. f. Augenh. **3**:361, 1900.

45. Fejér, J.: Ueber die Drusen des Sehnervenkopfes, Arch. f. Ophth. **72**:454, 1909.

46. Stood, W.: Zwei Fälle über Drusenbildungen am intraoculären Sehnervenende, Klin. Monatsbl. f. Augenh. **21**:506, 1883.

47. Mendel, F.: Ueber Drusenbildungen im Sehnervenkopf, Zentralbl. f. prakt. Augenh. **24**:242, 1900.

48. Rabitsch, F.: Zur Kenntnis der Drusen im Sehnervenkopf, Klin. Monatsbl. f. Augenh. **43**:72, 1905.

49. Shumway, E. A.: Hyaline Bodies on Optic Nerve Head, Tr. Coll. Physicians Philadelphia **38**:377, 1916.

50. Streiff, J. J.: Ueber Entstehung der Optikusdrusen, Klin. Monatsbl. f. Augenh. **42**:149, 1904.

Fejér,[45] Lordan,[51] Höeg,[11] Juler [36] and Reese.[2] In the case described by Juler central scotoma was also present. Enlargement of the blindspot has been frequently encountered with drusen. This is especially noteworthy, since it shows that enlargement of the blindspot cannot be relied on to differentiate papilledema from the pseudoneuritis produced by drusen of the optic nerve.

It is with particular interest that our attention is drawn to the association of drusen with changes in the fundus in which the optic disk alone is affected. Optic nerve atrophy was described by Müller,[1] Lauber,[5] Remak,[30] Stood,[46] Streiff [50] and Thomson.[52] Optic neuritis was reported by Stood,[46] Sachsalber [26] and Juler.[36] Pseudoneuritis was observed by Bonhoff.[53] Papilledema was recorded by Streiff,[50] Hirschberg and Cirincione [23] and Purtscher.[54] Any of the aforementioned alterations of the optic disk may be sufficiently great that the existence of an intracranial neoplasm must be seriously considered.

The not infrequent occurrence of headaches as a conspicuous symptom in cases of drusen of the optic nerve has previously received scant notice. A survey of the literature discloses that headaches were specifically mentioned as occurring in 6 cases reported by Jany,[55] de Schweinitz,[25] Höeg,[11] Oeller,[14] Stood,[46] and Cibis [34] and in 2 cases reported by Reese.[2] Our 2 cases may be added to this group; they clearly illustrate the clinical importance of appreciating the fact that drusen of the optic nerve may be associated with headaches so severe that the diagnostic possibility of a cerebral tumor must be seriously considered. This is even more true when the appearance of the optic disk is such as to be confused with that of optic neuritis or papilledema. No adequate explanation has been offered for the occurrence of these headaches, and we are unable to elucidate this problem at present.

SUMMARY AND CONCLUSIONS

The clinical records of a man and a woman with drusen of the optic nerves demonstrate the fact that this generally benign neuro-ophthalmologic disorder may at times be characterized by symptoms and signs which closely resemble those usually associated with tumor of the brain. Conspicuous among these clinical manifestations are (1) headache; (2) obscuring of the margins of the optic disk, with at times elevation of the disk, and (3) various alterations of the visual field, usually including enlargement of the blindspot.

Although further clarification is required in order accurately to define the origin of drusen, it is important to recognize the problem at times presented in differential diagnosis.

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DISCUSSION

DR. WILLIAM ZENTMAYER, Philadelphia: The accumulation of hyalin bodies on the head of the optic nerve is rare, and the scarcity of this condition makes worth while the report of cases. I have 2 such cases that I should like to put on record.

In the first case, a woman aged 23 was referred to me from Florida in May 1942. She had been under an ophthalmologist's care since July 1928. In 1931 there was an appearance of pseudopapillitis, but it was not until 1939 that the present condition was noted in its incipiency. In April 1942, the ophthalmologist gave in detail an accurate description of the condition. The visual fields were contracted and showed a number of reentering angles. Suspecting organic trouble, he had the patient given a thorough physical examination, which revealed a renal disturbance, the exact diagnosis of which was not stated, but the urine had persistently high albumin content, with blood cells.

The patient was normal mentally and presented no physical defects. Vision with correction was 6/4 part in the right eye and 6/6 part in the left eye. The intraocular tension was in the lower range of normal. Examination of the right eye revealed clear media, with a mass of hyalin matter, resembling a white mulberry, on the upper portion of the disk. The mass lay beneath the vessels, and there was some extension on to the retina. In the left eye, the appearance of the disk was similar, but the changes were not so conspicuous as those in the right eye. In both eyes the retinal arteries were too bright.

The visual fields showed considerable irregular contraction with great enlargement of the blindspot, the right field presenting several reentering angles and the left field but one. There could be little doubt that the condition was drusen of the nerve head. Similar anomalies of the fields have been noted before by other investigators, the explanation being that the mass makes pressure on the retinal fibers as they emerge from

51. Lordan, J. P.: Drusen of the Papilla, Am. J. Ophth. **15**:964, 1932.

52. Thomson, E. S.: A Case of Colloid Degeneration of the Optic Nerves, Post Graduate **14**:954, 1898.

53. Bonhoff, J. K.: Bericht über die Wirksamkeit der Universitäts—Augenklinik zu Giessen, Inaug. Dissert., Giessen, Kindt, 1906.

54. Purtscher, O.: Drusenbildung im Sehnervenkopf, Zentralbl. f. prakt. Augenh. **15**:292, 1891.

55. Jany, L.: Zur Casuistik der Drusenbildung in der Lamina vitrea chorioideae an der Papilla nervi optici, Zentralbl. f. prakt. Augenh. **3**:167, 1879.

the disk. As the history indicated that the condition was recently acquired and was progressive, there is a remote possibility that central vision may later be impaired by pressure on the papillomacular bundle of fibers.

In the second case the condition was more spectacular. A boy aged 9 years was referred by an ophthalmologist from New Jersey. The history was without significance. The child was somewhat undernourished, but there was no history of convulsions; his mentality was good, and there was no adenoma sebaceum. In the right eye the media were clear. Covering all but a narrow rim of the optic papilla, and extending somewhat below the lower border of the papilla on to the retina, was a heap of hyaline globular bodies. The size varied, but the average diameter was about that of a retinal vein, the larger ones being at the lower portion of the mass. The appearance of the whole was that of a white mulberry. The bodies were almost transparent and projected 5 D. into the vitreous. The level of the fundus was emmetropic. At the temporal border of the disk, the crystals were banked in two levels, and between the two the inferior temporal vein emerged. The nasal vein was pushed up somewhat at the edge of the disk. The rest of the fundus was normal. After homatropine had been instilled, the vision in the right eye, without a lens, was 6/6.

The fundus of the left eye presented no anomalies.

I have no recent notes regarding the progress in these cases. Mass drusen of the nerve are uncommon, as shown by the fact that the men who saw these 2 patients had had many years of experience in ophthalmoscopy, but apparently neither of them had ever seen such a condition.

The first patient had pseudo-optic papillitis. As the patient was under observation for several years before the appearance of the hyaline masses on the disk, it is possible that the pseudopapillitis observed in 1931 was due to the presence of these hyaline masses in the optic nerve and that later the increase became apparent on the surface of the papilla.

There should be no difficulty in diagnosing this condition, although in cases of tuberous sclerosis the gross ophthalmoscopic appearance is similar, sometimes even having been described as "mulberry-like"; if only a single lesion involves the nerve head, the resemblance is close. However, the general symptoms of tuberous sclerosis at once clear up the diagnosis.

DR. NATHAN S. SCHLEZINGER, Philadelphia. It is the case in which the drusen are more deeply situated and the appearance of the fundus resembles pseudoneuritis that presents the neurologic problem, especially if headaches of the type present in the second case are prominent. In such cases there may be elevation of the optic disk and enlargement of the blindspot, but drusen are not visible ophthalmoscopically.

UVEITIS ASSOCIATED WITH HODGKIN'S DISEASE

REPORT OF A CASE

SAMUEL KAMELLIN, M.D.
CHICAGO

Uveitis associated with Hodgkin's disease has not, to our knowledge, been reported previously in the literature. Uveitis associated with Boeck's sarcoid (sarcoidosis) has been noted.

Hodgkin's disease [1] is of interest because the etiologic factor is unknown; the condition has been called (1) an atypical form of tuberculosis, (2) an infection, (3) a tumor and (4) a transition between a granuloma and a tumor.

Clinically the disease may appear between the ages of 6 months and 76 years. It is most common, however, between the third and the fourth decade of life and occurs twice as frequently in men as in women. The average duration of the disease is eighteen months, but in the chronic form it may last for years.

It is usually thought of as a condition affecting the lymph glands of the neck, but involvement of the abdominal and thoracic nodes is more frequent. The spleen is involved in 60 to 75 per cent of cases. The blood picture shows a progressive anemia, with no change in the leukocytes and sometimes an increase in the eosinophils.

The differential diagnosis is made by examination of an involved lymph node, and the diseases to be considered are glandular tuberculosis, lymphosarcoma and Boeck's sarcoid.

Microscopically the essential change is a proliferation of the reticuloendothelial cells, which gradually replace the lymphocytes. The new cells are large and pale, with vesicular nuclei of the epithelioid type. More characteristic are the large giant cells, many of which are mononuclear and many multinucleated. These giant cells are known as Dorothy Reed cells, or Sternberg cells. The feature which distinguishes Hodgkin's disease from lymphosarcoma is the involvement in the latter of one group of nodes, with the subsequent spread of the condition by direct continuity to another group of lymphoid structures.

Microscopically lymphosarcoma shows complete replacement of mature lymphocytes by much larger, hyperchromatic cells with a small amount of basophilic cytoplasm and a round or oval nucleus with a fairly prominent nucleolus. Uniformity of cell type is an outstanding feature, in contrast to the multiplicity of cell forms present in Hodgkin's disease. In addition to lesions of the lymph nodes, the lymphoid tissue in the pharynx, gastrointestinal tract, spleen, bone marrow, liver and other organs is widely involved. The blood picture is that of a progressive secondary anemia, but there may be relative or absolute lymphocytosis.

In tuberculosis the typical cell is the epithelioid cell, which forms the principal part of the tubercle.

The clinical picture in Boeck's sarcoid simulates that of Hodgkin's disease. This condition is known to involve the uveal tract of the eye and the skin, lymph nodes, myocardium, pancreas, tonsil, parotid and lacrimal glands. The lesions are circumscribed masses resembling miliary tubercles, the chief components of which are epithelioid cells, with macrophages, giant cells and occasional eosinophils. The giant cells are larger than those of tuberculosis and contain more nuclei.

The roentgenographic features of Hodgkin's disease and of lymphosarcoma are enlargement of the hilar glands, with no involvement of the substance of the lungs; those of tuberculosis are infiltration and cavity formation, involving usually the apexes and bases of both lungs. In sarcoidosis the infiltration is along the bronchial tree and simulates most closely the picture of miliary tuberculosis.

REPORT OF CASE

Mr. C. D., aged 26, was admitted to the service of Dr. Sanford R. Gifford at Wesley Memorial Hospital on March 25, 1943. His complaint was that of failing vision for the past three months. At first he could not make out faces of people he knew and later was unable to read the newspaper. Three to four weeks prior to his admission to the hospital for this trouble, he went to his family physician because of a swelling in his neck. His physician advised that he go to the

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The late Dr. Sanford R. Gifford advised me in the report of this case.

From the Department of Ophthalmology, Northwestern University Medical School.

1. Boyd, W.: The Pathology of Internal Diseases, ed. 3, Philadelphia, Lea & Febiger, 1940.

hospital for surgical removal of a gland from the mass for pathologic study. Biopsy revealed considerable fibrosis and some hyalinization of fibrous tissue. Dorothy Reed cells and a few eosinophils were scattered throughout the section. The pathologist's diagnosis was chronic Hodgkin's disease (fig. 1).

lamp revealed cells in the anterior chamber and pigment and cell deposits on the anterior capsule of the lens. The patient was given a solution of scopolamine to use; after he stopped taking the drug, his pupils decreased in size and became adherent to the anterior capsule of the lens. The pupils were then dilated with

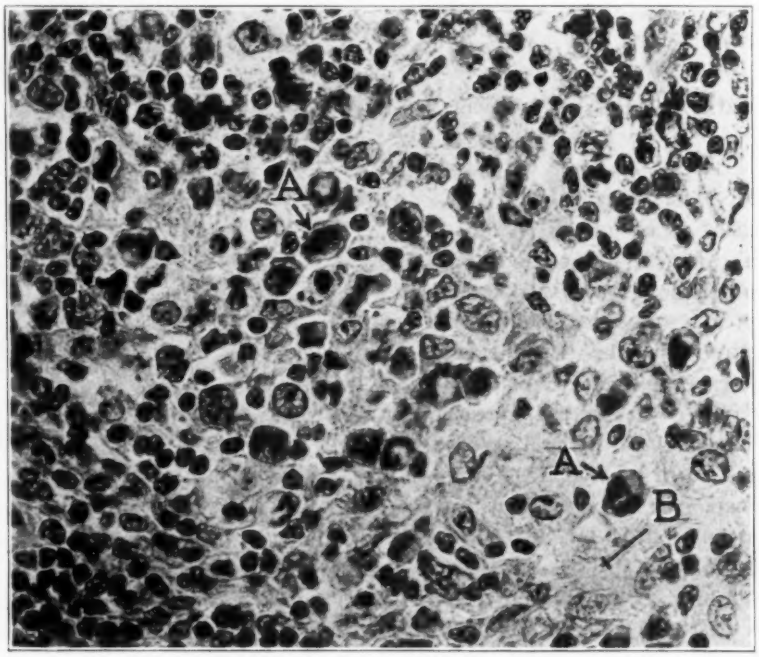

Fig. 1.—Section of a cervical lymph node, showing (*a*) Dorothy Reed cells and (*b*) fibrosis.

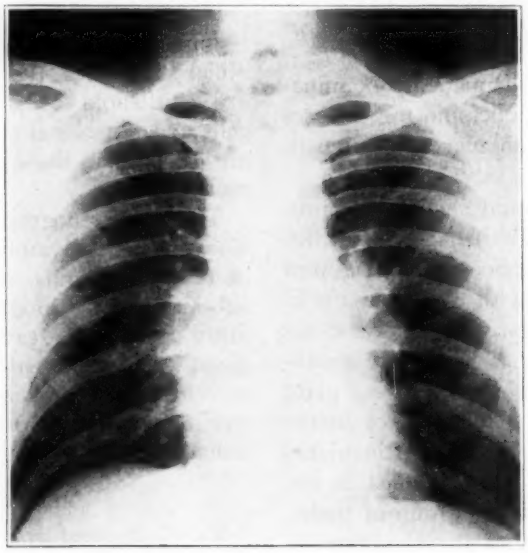

Fig. 2.—Roentgenogram of the patient's chest, showing involvement of the hilar lymph nodes. The apexes and the peribronchial regions are infiltrated.

Roentgenograms of the chest revealed the changes typical of Hodgkin's disease of the hilar lymph nodes (fig. 2).

Previous to his admission to the hospital, he was seen by Dr. Gifford in his office. Examination with the slit

neosynephrine and were kept free by administration of small doses of scopolamine. During this interval there was mild superficial and deep congestion of the vessels.

On his admission to the hospital, visual acuity was limited to ability to count fingers at 1 foot (30 cm.)

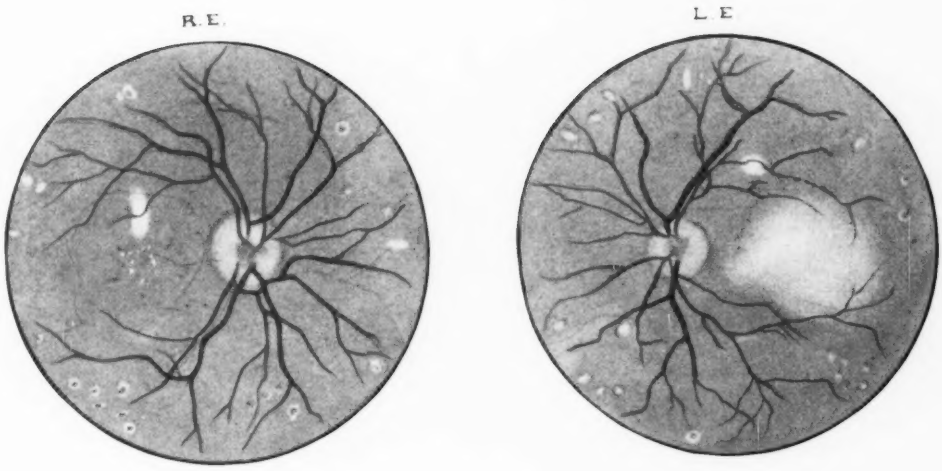

Fig. 3.—Drawing, showing large gray areas in the macular regions, with white deposits in the periphery of each fundus.

with the right eye and was 1/50 in the left eye. External examination revealed nothing abnormal. Examination of the fundi and media by Dr. Gifford revealed a great number of opacities in the vitreous of both eyes. Large gray areas were present in both macular regions; no vessels were visible. There were also many small white deposits in the periphery of each fundus. Above the left fovea was a small white area which elevated the vessels near it (fig. 3).

General physical examination showed essentially nothing unusual except for the presence of a small scar on the neck where the gland had been removed. The mass previously observed in the neck was gone, its disappearance being attributed to the roentgen ray therapy which he had received.

The red blood cells numbered 5,340,000 and the white blood cells 13,350 per cubic millimeter, and the hemoglobin concentration was within normal range. Urinalysis gave normal results.

The Frei, brucellin and tuberculin cutaneous tests gave negative reactions.

The patient was placed under treatment with nonspecific foreign protein, typhoid and vaccine paratyphoid A and B being given. On his discharge from the hospital visual acuity was 8/50 in the right eye and 1/50 in the left eye, values showing improvement in the right eye and no appreciable improvement in the left eye.

The patient has since been followed closely, and on his last examination, on Dec. 16, 1943, visual acuity was 6/200 in the right eye and 3/200 in the left eye. At the time of writing the vitreous still shows many opacities. There are still large grayish areas in the macular regions from which finger-like processes extend into the vitreous. A number of flat, white areas in the periphery and macular regions resemble those seen in cases of miliary tuberculosis.

General examination of the palpable lymph glands has revealed no further enlargement to date, and the patient's condition is good.

Whether the uveitis accompanying Hodgkin's disease in this case is due to the latter condition or is a concomitant disease is not clear. Since, however, the tests and examinations did not reveal any positive indication of other disease and there is pathologic and roentgenographic evidence of Hodgkin's disease, we are inclined to believe that the ocular condition is due to Hodgkin's disease.

UVEITIS; DYSACOUSIA; ALOPECIA; POLIOSIS, AND VITILIGO

A THEORY AS TO CAUSE

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Because the most disabling manifestation of the rare disease complex under consideration is ocular, it is not surprising that the syndrome has been discussed chiefly in the ophthalmologic literature. Still, the existence of the syndrome, and certain aspects of it which have not always been widely recognized, demonstrate the relevance of systemic and ocular disease. The repeated occurrence of the disease pattern should interest the nosologist, who still must hesitate to designate it as a disease entity, when most or all of the same clinical picture may follow severe emotional trauma, expansion of an ependymoma of the third ventricle and, frequently, transient encephalitis. Certainly, the subject is of interest to the internist, the dermatologist and the neurologist.

In this paper the historical background of the syndrome is briefly reviewed. A general description of the disease picture is presented, including the fact that the prodrome may be essentially either an encephalitis or a severe emotional disturbance, the latter suggesting the possibility of hypothalamic involvement, which if present is of far reaching interest. A remarkably similar clinical picture has been produced by impingement of a tumor of the third ventricle on the hypothalamus. A case of the syndrome is presented, with photographs taken with ultraviolet light showing the vitiligo. Certain manifestations involving the skin are shown to be associated with other disease states, to be, in all probability, true dermatoneuroses, and to be comparable to depigmentation affecting the eye in this syndrome. The "depigmentation" of ocular tissue constitutes a disturbance of pigment deposit more severe and more generalized than is common with sarcoma of the choroid; and since the latter lesion has, even before 1878, been known to cause sympathetic ophthalmia,[1] it is suggested that the inflammatory disease picture in the eye in this syndrome, remarkably similar to that observed in sympathetic ophthalmia, is secondary to pigment changes. Lastly, the basis for the belief that the hypothalamus may be the primary seat of the syndrome is presented, and evidence that a virus may cause the hypothalamic involvement is referred to. The results of cisternal inoculation of rabbits with material taken from the patient's eye over a year after the acute stage of the disease are mentioned.

HISTORICAL REVIEW

Depigmentation of the cilia and eyebrows, frequently sudden, and following supraorbital neuralgia, painful trauma or nontraumatic severe intraocular inflammation, has long intrigued ophthalmologists. The earliest reference to whitening of the cilia which I have found is that of Ali ibn Isa, whose text Wood [2] imputed to the period 940-1010 A. D. Considerably later (in the twelfth century) another Arab physician,[3] referred to by Babel [4] and others, in dealing with the historical aspect of the syndrome, mentioned canities in a list of thirty-seven apparently common ocular disorders. Schenkl [5] was the first to report its appearance during the course of "sympathetic ophthalmia." Other early papers on the subject have been reviewed by Babel,[4] who did not refer specifically to Jonathan Hutchinson's [6] account, in 1892, of "blanched eyelashes"

Read at the meeting of the Medical Society of the State of New York, Section on Ophthalmology and Otolaryngology, Buffalo, May 5, 1943.

1. (*a*) Duke-Elder, W. S.: Text Book of Ophthalmology, St. Louis, C. V. Mosby Company, 1941, vol. 3, p. 2329-2332. (*b*) Mauthner, L.: The Sympathetic Diseases of the Eye, translated by W. Webster and J. A. Spalding, New York, W. Wood & Co., 1881, p. 44.

2. Wood, C. A.: Memorandum Book of a Tenth-Century Oculist for the Use of Modern Ophthalmologists: A Translation of the Tadhkirat of Ali Ibn Isa of Baghdad (cir. 940-1010 A. D.), the Most Complete, Practical and Original of All the Early Textbooks on the Eye and Its Diseases, Chicago, Northwestern University, 1936, p. 102.

3. Mohammad, Al-Ghâfiqi: Le guide d'oculistique: 1100-1200 A. D., translated by M. Meyerhof, Barcelona, Laboratories du Nord de l'Espagne Directeur, Masnou, 1933, pp. 22 and 46.

4. Babel, J.: Syndrome de Vogt-Koyanagy (uvéite bilaterale, poliosis, alopecie, vitiligo et dysacousie), Schweiz. med. Wchnschr. **69**:1136, 1939.

5. Schenkl, A.: Ein Fall von plötzlich aufgetretener Poliosis circumscripta der Wimpern, Arch. f. Dermat. u. Syph. **5**:136, 1873.

6. Hutchinson, J.: A Case of Blanched Eyelashes, Arch. Surg., London **4**:357, 1892-1893.

in cases of severe bilateral uveitis, the earliest mention of the subject in English.

From that time, various authors have made similar observations, sometimes associating the uveitis, which is more or less severe,[7] and the depigmentation of the cilia and superciliary region with difficulties of hearing and with alopecia areata, which is followed by regrowth of hair, now white, in the involved areas. Koyanagi,[8] in 1929, summed up the observations of 14 Japanese authors in tabular form, and subsequently histologic and bacteriologic studies have appeared in their literature. Parker[9] in 1931, published the first description in the English language except for Hutchinson's brief note; he summarized 19 cases, including 2 of his own, and cogently commented that "the [reported] incidence of neuroretinitis and detached retina may be far from correct, as a satisfactory fundus examination is impossible in many cases." He commented on the similarity of the syndrome to sympathetic ophthalmia, in which a similar uveal involvement may appear and in conjunction with which alopecia, poliosis and deafness have been reported. He extended his comments in a review,[10] published in 1940.

Rones,[11] in 1932, published 3 typical cases. He stated that a scratchy feeling often precedes the uveitis in this disease. His observation is confirmed in the case reported here, in which to the patient it seemed a prominent feature of the prodrome.

Davies,[12] in the presentation of a case, succinctly reviewed the etiologic theories which have been proposed. As he stated, the result has usually been negative when tuberculin and Wassermann tests have been performed. The theory submitted by Peters[13] and by Cramer,[14] that anaphylactic toxins formed by the destruction of uveal pigment cause the manifestations in the skin, hair and ear, has little to recommend it beyond the fact that pigmentary changes do occur in the skin and hair and that similar changes might occur in certain pigmented structures in the cochlea. It does not account for the prodromal encephalitis, or explain why, if the eye were the seat of the primary lesion, apparently similar intraocular disease in other forms of uveitis does not involve the hair, skin and ears. While Cramer reported that intravenous injections of blood from affected subjects into rabbits produced poliosis in these animals, any such changes might be explained on an infective basis.

In 1939 Babel[4] collected 46 cases of the syndrome. A number of these cases, particularly the earlier ones, do not seem entirely typical, but it may be that some of them were not completely reported. It is certain that the constellation of bilateral uveitis, dysacousia, alopecia areata, poliosis and vitiligo appears too constantly to be regarded as simple coincidence.

Since that time cases have been reported by Zentmayer[15] and by Carrasquillo.[16]

GENERAL DESCRIPTION

The ensemble of symptoms is too consistent to suggest a heterogeneous pathogenesis. Just as in other clearly defined disease states certain manifestations may atypically be added to, or be absent from, the clinical picture in individual cases, so with this syndrome abbreviated versions have been reported, some of these variants shading into significantly related disease. The syndrome bears striking resemblance in certain respects to Harada's disease (bilateral detachment of the retina associated with low grade uveitis) and to sympathetic ophthalmia.

In the earlier case reports medical observers appear to have been more frequently aware of the severe uveitis and the striking poliosis than of the alopecia, vitiligo or dysacousia. Other manifestations equally typical of the syndrome, and probably equally significant, have received still less attention.

It is likely that many cases of the apparently incomplete syndrome were actually cases of the fully developed disease, meagerly reported. Some of the symptoms associated with this syndrome do not present themselves dramatically to either patient or physician and may have been overlooked in some instances. Other relevant aspects are mentioned in careful case reports without

7. Compare the related syndrome Harada's disease.

8. Koyanagi, Y.: Dysakusis, Alopecia und poliosis bei schwerer Uveitis nicht traumatischen Ursprungs, Klin. Monatsbl. f. Augenh. **82**:194, 1929.

9. Parker, W. R.: Uveitis Associated with Alopecia, Poliosis, Vitiligo and Deafness, Am. J. Ophth. **14**:577, 1931.

10. Parker, W. R.: Severe Uveitis with Associated Alopecia, Poliosis, Vitiligo and Deafness, Arch. Ophth. **24**:439 (Sept.) 1940.

11. Rones, B.: Uveitis with Dysacousia, Alopecia and Poliosis, Arch. Ophth. **7**:847 (June) 1932.

12. Davies, W. S.: Uveitis with Associated Alopecia, Poliosis, Vitiligo and Deafness, Arch. Ophth. **14**:239 (Aug.) 1935.

13. Peters, A.: Die Diagnose und Therapie der sympathischen Augenentzündung, Deutsche med. Wchnschr. **38**:1361, 1912; cited by Davies.[12]

14. Cramer, E.: Zur Frage der anaphylaktischen Entstehung der sympathischen Entzündung, Klin. Monatsbl. f. Augenh. **51**:205, 1913.

15. Zentmayer, W.: Severe Uveitis with Associated Alopecia, Poliosis, Vitiligo and Deafness, Arch. Ophth. **27**:342 (Feb.) 1942.

16. Carrasquillo, H. F.: Uveitis with Poliosis, Vitiligo, Alopecia and Dysacousia (Vogt-Koyanagi Syndrome), Arch. Ophth. **28**:385 (Sept.) 1942.

being given significant emphasis or being considered related to the illness. None the less, there is a good deal of variation in the severity and inclusiveness of the syndrome, and cases have been reported in which one or more of the classic features have on careful search proved to be absent.[17]

It is even probable that abortive cases do occur. In addition to the case here reported (of the complete syndrome), it has been my privilege, through permission of Dr. John Dunnington, to study a case in which only much less severe uveitis, retinal detachment and poliosis of the cilia and brow were present. When the plastic iritis is more striking, the similarity to sympathetic ophthalmia is greater, and it is historically interesting that numerous observers have noted the clinical resemblance.[12]

In typical cases the first symptoms to appear are ocular, sometimes a scratchy feeling being first noticed in the eyes, as Rones[11] reported and as was noted in the case to be described here, followed by lowering of visual acuity. In a number of cases in which the fundus has been observed in an early stage of the disease, papillitis and retinal edema, choroidal disturbance and day blindness have been observed. Opacities, generally fine, appear in the vitreous; and anterior uveitis develops, with keratitic precipitates, seclusion and occlusion of the pupil. The plastic exudate in the anterior chamber may be pronounced. The iridocyclitic reaction persists in its inflammatory phase for months, terminating in pronounced atrophy of the pigmented structures, as shown by transillumination or ophthalmoscopic examination. Because of the intense intraocular damage, in the more severe forms of the disease visual acuity does not improve, and even if phthisis bulbi does not appear, as it often does, virtual or complete blindness is the end result in most cases. It is my impression that the degree of severity of the intraocular process tends rather uniformly to be equal in the two eyes of the individual patient. Secondary glaucoma or retinal detachment may be encountered.

In both typical and, as it were, abortive cases there is, time and again, a prodrome of an influenza-like episode.[18] But in a case reported by Laje Weskamp,[19] in which the influenzal prodrome was not present, transcendent emotional trauma immediately preceded the onset of the disease. The fact that all, or practically all, the manifestations of this syndrome have followed (*a*) an infection of the upper respiratory tract suggesting encephalitis, (*b*) severe emotional trauma or (*c*) a tumor pressing on the hypothalamus deserves later comment.

As early as 1890, Bock[18a] reported a case of optic nerve atrophy occurring ten days after an attack of "influenza" and suggested that transient localized meningitis in the region of the chiasm was responsible for the nerve lesion. In this case, as in others,[20] poliosis of the cilia developed after an initial attack of influenza.

The "influenza" in the more completely reported cases appears to have been encephalitis.[21] Since persistent headaches,[21a] drowsiness, unmitigated by ordinary medication, gastrointestinal upset with vomiting, fever,[22] and even delirious shivering,[23] were present, a positive Queckenstedt sign would appear characteristic of this stage (it may be assmed that a block in the circulation of the cerebrospinal fluid accounts for the cephalgia). The presence of hypercholesteremia and hyperglycemia has been reported.[24] At this stage, in 1 case, a roentgenogram gave evidence of increased intracranial pressure.[23a]

17. (*a*) Jess, A.: Poliosis, Vitiligo, und doppelseitige schwerste Iridocyclitis bei Dystrophia adiposo-genitalis, Ber. ü. d. Versamml. d. deutsch. ophth. Gesellsch. **49**: 469, 1932. (*b*) Koyanagi.[8]

18. (*a*) Bock, E.: Ueber frühzeitiges Ergrauen der Wimpern, Klin. Monatsbl. f. Augenh. **28**:484, 1890. (*b*) von Michel, J.: Die Krankheiten der Augenlider, in Graefe, A., and Saemisch, E. T.: Handbuch der Augenheilkunde, ed. 2, Leipzig, Wilhelm Engelmann, 1908, vol. 5, pt. 2, p. 294. (*c*) Jess.[17a]

19. Laje Weskamp, R.: Uveitis exudativa bilateral con disacusia, poliosis, alopecia y desprendimiento retiniano, Rev. Asoc. méd. argent. **46**:1451, 1932.

20. Jess.[17a] von Michel.[18b]

21. (*a*) Krasnoff, M. L.: Uveitis, Vitiligo, Poliosis, Dysacousia, in Sbornik v oznamenovanie sorokaletiya nauchnoy deyatelnosti zasluzhennogo deyateya nauki M. I. Averbakha, Moscow, Gosudarstvennoe izdatelstvo biologischeskoy i meditsinskoy literatury, 1935, p. 244; abstracted, Zentralbl. f. d. ges. Ophth. **37**:120, 1937. (*b*) Bunge, E.: Ueber doppelseitige Iridozyklitis und Poliosis, Arch. f. Augenh. **108**:212, 1933. (*c*) Calogero, G.: Sui disturbi auricolari nell'oftalmia simpatica, Arch. di ottal. **33**:499, 1926. (*d*) Avalos, E.: Un neuvo caso de uveitis bilateral grave acompañado de sordera, calvicie y canicie, Rev. cubana de oto-neuro-oftal. **1**:242, 1932; Mi tercera observación sobre un caso de uveitis bilateral grave, acompañado de sordera, calvicie y canicie, ibid. **5**:75, 1936. (*e*) Magitot, A., and Dubois-Poulsen, A.: Un cas de syndrome de Harada uvéite grave avec décollements bilatéraux et encéphalite, Bull. Soc. d'opht. de Paris **51**:223, 1939. (*f*) Soriano, F. J.: Sordera, calvicie y canicie an las uveitis bilaterales graves, simpáticaso no, Arch. de oftal. de Buenos Aires **4**:537, 1929. (*g*) Vonderahe, A. R.: Changes in the Hypothalamus in Organic Disease, A. Research Nerv. & Ment. Dis., Proc. **20**:689, 1940. (*h*) Babel.[4] (*i*) Bock.[18a]

22. Calogero.[21c] Magitot and Dubois-Poulsen.[21e]

23. (*a*) Yanes, T. R., and Ferrer, O.: Uveitis doble espontanea, con disacusia, alopecia y poliosis, Rev. cubana de oto-neuro-oftal. **7**:5, 1938. (*b*) von Michel.[18b]

24. Aten, A. H.: Ueber Poliosis und Iridozyklitis, Ophthalmologica **97**:265, 1939.

In the few cases in which a spinal tap was performed shortly after the onset of the complaint which first brought the patient under medical observation, a rather pronounced pleocytosis was noted, but the spinal fluid has been examined early in too few instances of this rare disease for the establishment of more than the probability that pleocytosis will be found if searched for not long after the onset of the prodrome.[25] The case to be reported shows how transient this abnormality of the spinal fluid may be.

In some cases severe emotional trauma antedated the prodrome.[26] Its etiologic significance must be suspected in the sporadic cases in which circumstances, such as sudden dread of imminent death, either of the patient or of some member of the family, have been followed by rapid whitening of the hair, as in the imperfectly authenticated case of Marie Antoinette, or, within a few days, by the uveitis, complicated shortly by all the rest of the syndrome, including optic neuritis, retinal detachment, dysacousia, poliosis, alopecia and vitiligo. Parker [27] stated that it is not possible to determine how frequently retinal detachment and neuroretinitis occur in such cases, for frequently a satisfactory examination of the fundus cannot be made when the patient is first observed. In 1 case,[19] a laborer in the Argentine, falling into a deep pit, caught himself on a timber after falling a few feet and clung there for a good portion of an hour, without much expectation of rescue. When he was extricated, he was observed to remain in great terror, was "covered with cold sweat" and complained immediately of severe headache and tinnitus on the right side. In this case, in which the etiologic mechanism seems to have been functional rather than "influenzal," not only did the alopecia and dysacousia disappear, as they do in most cases, but the ocular manifestations, which ordinarily do not show recovery, here exhibited pronounced improvement. The retina became completely reattached, and vision improved from perception of light in either eye to visual acuity of 1/8 in the right eye and 1/6 in the left eye. Although recovery of this degree of vision may not appear striking, most patients with this symptom complex do not maintain more than ability to perceive hand movements.

When the signs of an encephalitic process are pronounced, there may be disturbance of the sleep rhythm, a complaint traceable to a lesion in the basal ganglions, which are held to mediate the various phenomena of sleep. The severity of the encephalitis at this stage appears to vary; often when the patient is first seen the presenting complaint is blurring of vision. If the patient is examined while the ocular media are still clear, a low degree of papillitis or depigmentation of the chorioretina may be observed.

Contraction of the visual fields [28] and night blindness [29] have been reported more frequently than have normal fields of vision or normal light sense. When it has been possible to observe the retina, pathologic processes (papillitis, retinal exudation and degeneration) sufficient to account for severe functional impairment have been seen.[30] Although it may appear difficult to classify the various retinal changes reported under one pathogenic heading, conspicuous depigmentation of the fundus has been repeatedly observed.[31] Franceschetti and Valerio [32] reported the association of heterochromia iridis with the dysraphic status and vitiligo. Other investigators mentioned the associated occurrence of heterochromia iridis.[33] When transscleral transillumination was employed, pronounced rarefaction of pigment was seen in all parts of the uvea except the ciliary zone.[19] This change was present in the case here reported. Soon the ocular picture is that of an anterior and a posterior uveitis. Seclusion or occlusion of the pupil, in greater or less degree, usually follows, and it is because many of the patients in the recorded cases were first seen at this stage that much uncertainty exists regarding the earlier neuroretinitis. Keratitic precipitates, floating bodies in the vitreous and seclusion and occlusion of the pupil, in greater or less degree,

25. (*a*) Malbrán, J., and Muhlmann, V.: Enfermedad de Harada, Cong. argent. de oftal. (1936) **2**:194, 1938. (*b*) Avalos.[21d] (*c*) Bunge.[21b] (*d*) von Michel.[18b] (*e*) Steindorff, K.: Vitiligo der Lider und Poliosis nach stumpfer Verletzung, Klin. Monatsbl. f. Augenh. **53**: 188, 1914.

26. Avalos.[21d] Yanes and Ferrer.[23a]

27. Parker, footnotes 9 and 10.

28. (*a*) Erdmann, P.: Zur Frage eines Zusammanhanges zwischen Vitiligo und Augenliden, Klin. Monatsbl. f. Augenh. **49**:129, 1911. (*b*) Laje Weskamp.[19] (*c*) Magitot and Dubois-Poulsen.[21e]

29. Laje Weskamp.[19] Avalos.[21d]

30. (*a*) Gilbert, W.: Vitiligo und Auge, ein Beitrag zur Kenntnis der herpetischen Augenerkrankungen, Klin. Monatsbl. f. Augenh. **48**:24, 1910; Ueber Bezeihungen der Gefässhaut zu endokrinen Störungen, Ber. ü. d. Versamml. d. deutsch. ophth. Gesellsch. **48**:26, 1930. (*b*) Laje Weskamp.[19] (*c*) Magitot and Dubois-Poulsen.[21d] (*d*) Soriano.[21f]

31. (*a*) Komoto, J.: Ueber Vitiligo und Auge, Klin. Monatsbl. f. Augenh. **49**:139, 1911. (*b*) Wexler, D.: Ocular Depigmentation Accompanying Generalized Vitiligo, Arch. Ophth. **57**:393, 1928. (*c*) Babel.[4] (*d*) Laje Weskamp.[19] (*e*) Magitot and Dubois-Poulsen.,[21e] (*f*) Erdman.[28a]

32. Franceschetti, A., and Valerio, M.: L'uveite recidivante (ad ipopion) manifestazione parziale di una sindrome muco-cutaneo-oculare, Rassegna ital. d'ottal. **9**:1, 1940.

33. Erdmann.[28a] Babel.[4]

usually follow.[34] In some, but not in all, cases there is retinal detachment.[35]

Late in the course of the disease examination with the corneal microscope and the slit lamp has shown marked atrophy of the iris, with dispersion of pigment.[21c] This lesion was also conspicuous in my case. Whether the heavy posterior synechia indicates an inflammatory, as well as a degenerative, process merits study and consideration.

By this time the dysacousia, which may occur as early as during the prodromal stage of encephalitis, is usually a source of discomfort to the patient. It consists of usually partial, and often unilateral, deafness, which may persist for several months but which tends to disappear, and of a troublesome ringing in the ears, often unilateral, which lasts longer.

The results of laboratory studies, except those of the spinal fluid, are negative consistently enough to minimize any importance attached to an occasional positive Wassermann reaction [12] or a positive diagnostic tuberculin reaction.

One to three months after the onset of the disease alopecia similar to, or identical with, alopecia areata appears, followed usually, and with the same frequency as is alopecia areata, by poliosis. Although whitening of the hair in a piebald manner is not uncommonly associated with alopecia areata, in cases of this syndrome many of the hairs of the brow and many of the cilia are involved, and occasionally [19] other regions of the body hair are included in this process. The vitiligo usually appears about the time of, or a little after, the alopecia. The fact that the vitiligo is not always conspicuous under ordinary illumination may account for its later recognition, historically, in cases of this syndrome. In a number of early cases the patient came under medical observation rather late in the disease, and this may account for the fact that in these cases alopecia was not mentioned.

As the regrowth of hair occurs in the affected areas, it tends to be white. This, and the generalized vitiligo described by Gilbert,[30a] which is likely to occur broadly in the region of the depigmented brow, as well as on the trunk,[36] or even on the extremities, give the patient a striking and bizarre appearance, which, together with blindness, is apt to cause him much concern. The progress is gradual, extending over many months. In 1 case, a daughter of the patient showed premature graying of the hair, and there was a family history of poliosis.

As previously stated, the changes in the eyes are progressive, and it is months before the uveitis, which varies in severity and is sometimes complicated by secondary abnormalities of intraocular tension, begins to subside.

During the active course of the disease, and later, severe disturbances of temperature sensation have been reported.[37] Previously the cryesthesia had been interpreted as hysterical. In 1 of Gilbert's cases, that of a man aged 35, libido and potency were entirely lost, suggesting hypothalamicohypophysial involvement. Perhaps only apparently relevant to this discussion is Jess's [17a] case, an instance of typical dystrophia adiposogenitalis.

RELATION OF MANIFESTATION

Alopecia.—Alopecia may be due to local disease of the skin [38] or may be secondary to severe systemic illness, or in the form in which it is seen in this syndrome (typical alopecia areata) it was included by Becker and Obermayer [39] among the dermatoneuroses. Parker,[27] similarly, listed the causes of alopecia as infection, reflex neurosis or endocrine disturbance. McCarthy [38] stated that alopecia, of nervous origin, may be the essential primary lesion or may be secondary to atrophic changes in the skin. It is noteworthy that loss of hair following severe systemic illness is frequently a delayed manifestation. It is likely, as Stokes [40] emphatically stated, that "the interplay between emotion and infection, emotion and allergy, emotion and sweat, and vasomotor mechanisms, furnish some of the most complicated of the present problems of increasing importance. . . ." Niles [41] and Becker and Obermayer included alopecia [39] among the dermatoses of neurogenic origin.

McCarthy [38] stated that the actual cause of alopecia is not known. According to him, Bärnsprung suggested as early as 1858 that alopecia may be due to nutritional disturbances of the hair papilla resulting from derangement of trophic nerves serving it. He referred to the work of Joseph and others, who produced alopecia in

34. Magitot and Dubois-Poulsen.[21c] Gilbert.[30a] Komoto.[31a]

35. Magitot and Dubois-Poulsen.[21c] Soriano.[21f] Koyanagi.[8]

36. Luo, T. H.: Uveitis Associated with Alopecia, Poliosis, Dysacousia, and Vitiligo, Chinese M. J. **50**: 1409, 1936.

37. Yanes and Ferrer.[23a] Avalos.[21d] Magitot and Dubois-Poulsen.[21c]

38. McCarthy, L.: Diagnosis and Treatment of Diseases of the Hair, St. Louis, C. V. Mosby Company, 1940, pp. 63 and 137.

39. Becker, S. W., and Obermayer, M. D.: Modern Dermatology and Syphilology, Philadelphia, J. B. Lippincott Company, 1940, p. 533.

40. Stokes, J. H.: Personality Factor in Psychoneurogenous Reactions of the Skin, Arch. Dermat. & Syph. **42**:780 (Nov.) 1940.

41. Niles, N. D., in discussion on Stokes.[40]

experimental animals by section and removal of the sympathetic trunks. Stokes and his associates [42] summarized current criticism of Joseph's technic but concluded that there is a gradually increasing accumulation of evidence that a neural mechanism plays a causative role in loss of hair. That the familiar association of functions of the endocrine and the vegetative nervous system is involved in the production of alopecia, as well as poliosis and vitiligo, is confirmed by the opinion expressed by Genner,[43] McCarthy,[38] Stokes and associates,[42] Becker and Obermayer [39] and others. Von Weo, cited by von Michel,[18b] reported the association of alopecia of the lids with exophthalmic goiter, and Genner pointed out that alopecia frequently occurs with exophthalmic goiter, in certain nervous diseases, disturbances of the vegetative nervous system and after trauma and shock. Galewsky [44] stated that children of parents with exophthalmic goiter often show alopecia or vitiligo or both. There is a considerable literature relating to the endocrine background of alopecia, poliosis and vitiligo.[45] Wyss [46] recorded both alopecia and vitiligo in the affected areas in cases of herpes zoster. Terrien [47] mentioned the association of alopecia and cataract. Alopecia areata has been reported to be associated with syringomyelia and progressive facial hemiatrophy.[48] In a case of alopecia reported by Vonderahe [21g] the hypothalamus showed significant changes. Von Michel [18b] stated that alopecia neurotica may be accompanied by poliosis and may follow local trauma. Donath [49] observed local erythema of the skin and falling of the hair after excision of a segment of a sympathetic nerve. Becker,[50] in a personal communication, suggested that in the case which I am reporting the alopecia is probably neurogenic.

Poliosis.—Poliosis, or canities, is a premature bleaching or whitening of the hair; it may affect all the lashes of one or both eyes or be confined to a small number of cilia. Frequently the eyebrows show a similar depigmentation. The hair of the head and of the body generally may be involved. A good deal has been written about the biochemical change in the hair tissue, and the most complete monograph on this subject is that of Schreiber.[51]

McCarthy [38] maintained that sudden graying of the hair was produced by rapid penetration of the hair by air, a vacuolation ascribed to neural influence; Steindorff [25e] confirmed this in his case, but Vogt [52] could not. Certain forms of poliosis, at least, are considered to be due to inhibition of pigment formation in the cortical cells of the hair-bearing skin.

McCarthy [38] distinguished between "true poliosis," which is permanent, and canities due to alopecia areata, which (frequently) is not permanent. This distinction serves to emphasize the fact that poliosis is frequently, but not always, an accompaniment of, or secondary to, alopecia areata. The causal relation of poliosis and vitiligo has been suggested here.

A survey of many reported cases of graying hair shows that frequently no mention is made of the rapidity of the process or of the duration of the change in color. Poliosis has been observed to occur in persons of all age groups; it has been reported in children 5 years of age.[53] To distinguish between "true poliosis" and secondary poliosis on the basis of permanence is somewhat empiric. Although Oesterlen,[54] as recently as 1931, stated that graying or whitening of the hair occurring overnight or in the course of several days has never been established, and is, in his opinion, impossible, there appears to be sufficient reason to believe that a sudden whitening of the hair does occur. Although some of the earlier instances, such as the case of Marie Antoinette, have been reported by witnesses whose reliability cannot be determined

42. Stokes, J. H.; Beerman, H., and Ingraham, N. R., Jr.: Psychoneurogenous Component of Cutaneous Reaction Mechanisms, Am. J. M. Sc. **198**:577, 1939; **200**:560, 1940.

43. Genner, V.: Études clinique sur la pelade, Copenhagen, Levin & Munksgaard, 1929; cited by Stokes.[40]

44. Galewsky, E.: Beiträge zur Kenntnis Alopecia areata, Dermat. Wchnschr. **81**:1327, 1925.

45. Bauckus, H. H.; Siekmann, C. F., and Kwak, A. V.: Treatment of Alopecia Areata with Thyroid Extract, New York State J. Med. **36**:1629, 1936.

46. Wyss, O.: Beitrag zur Kenntnis des Herpes Zoster, Arch. d. Heilk., 1871, p. 261.

47. Terrien, F.: Troubles visuels et altérations des glandes á sécrétion interne, Arch. d'opht. **39**:716, 1922.

48. Satke, O.: Ueber das Ergrauen der menschlichen Körperbehaarung, Ztschr. f. Konstitutionslehre **15**:646, 1930.

49. Donath, J.: Der Werth der Resection des Halssympathicus bei genuiner Epilepsie, nebst einigen Beobachtungen und physiologischen Versuchen über Sympathicuslähmung, Wien. klin. Wchnschr. **11**:383, 1898.

50. Becker, S. W.: Personal communication to the author.

51. Schreiber, L.: Die Krankheiten der Augenlider, ed. 3, Berlin, Julius Springer, 1924.

52. Vogt, A.: Frühzeitiges Ergrauen der Zilien und Bemerkungen über den sogenannten plötzlichen Eintritt dieser Veränderung, Klin. Monatsbl. f. Augenh. **44**:228, 1906.

53. Rindfleisch: Ein Fall von einseitgem Ergrauen der Wimpern bei einem Kinde, Klin. Monatsbl. f. Augenh. **40**:53, 1902.

54. Oesterlen, O.: Plötzliches Haarergrauen nach psychischen Insult, Med. Welt **1**:1472, 1927; **5**:1129, 1931.

and Oesterlen stated that no case of sudden whitening of the hair was noted during World War I, sudden poliosis was reported on the basis of first hand medical observation among the Italian air forces.[55]

Bowman[56] stated that "well authenticated instances have occurred in which hair has grown white in a single night, from the sudden influence of some depressing passion." Several well established cases of sudden whitening of hair were reported by Klauder.[57] In 1 of these, a man aged 35 was harassed for a week by the thought that an inexcusable mistake which he had made might result in heavy loss of life aboard a troop ship. He was seen by his associates the night before an official investigation, when no change was noticed in his appearance. The next morning he was shaved by a barber and did not know that his hair had changed color until he arrived at his office, when fellow workers exclaimed, "What is the matter with your hair; it is snow white!"

Landois[58] reported a similar case of rapid whitening of the hair in a man aged 35 who experienced severe terror during delirium tremens. Ornsteen[59] mentioned the case of a woman aged 30 whose hair became entirely white within three hours when she was informed that her child had been run down by a truck. MacLeod[60] described poliosis associated with vitiligo following severe emotional shock. Roose[61] recounted the case of a girl aged 17 whose eyelashes turned white overnight following fright.

Among the cases listed[50] as instances of spontaneous whitening of the hair are several[62] in which only the cilia were involved, and some other pathologic process was present which might involve nerve channels. In other cases, such as that of Rindfleisch,[53] no other complicating factor was disclosed. In my opinion, the nervous origin of poliosis is substantiated by numerous reports of cases of poliosis following trigeminal neuralgia,[63] traumatic wounds,[64] iridocyclitis, nerve injuries[47] and peripheral neuritis[47]; associated with pain in the region innervated by the right trigeminal nerve,[63a] interstitial keratitis and iridocyclitis,[65] and after operations on the eye which were notably painful.[66] In these cases the poliosis was limited to the region of the nerve trunk involved.

Schenkl[5] discovered several silvery white lashes on the temporal half of the left upper lid of a boy aged 9 years, at a time when the eye was sympathetically inflamed in consequence of an injury received by the right eye. On the right upper lid all the lashes were perfectly white except for a minute portion of the tips, which were very dark.

Jacobi[64b] also noted in an eye sympathetically affected with iridocyclitis that the lashes of the nasal half of the upper lid were snow white, while those on the outer half of the same lid were black and white in about equal proportions, the lower lid presenting merely a few white hairs.

That the neurotropic origin of poliosis must be considered in a broader sense is indicated by the cases in which it has occurred after a severe emotional trauma, such as in the case of Hutchinson,[6] the recent case of the complete syndrome reported by Laje Weskamp[19] and the cases of poliosis remarkable for the sudden-

55. Vignolo-Lutati, C.: Canizie precoce e psicopatie di guerra, Policlinico (sez. prat.) **25**:680, 1918.

56. Bowman, W.: The Collected Papers of Sir William Bowman, London, Harrison & Sons, 1892, vol. 1, p. 150; originally published by Todd, R. B., and Bowman, W.: Physiological Anatomy and Physiology of Man, Philadelphia, Blanchard & Lea, 1857, vol. 1, chap. 14, pp. 406-426.

57. Klauder, J. V.: Sudden Whitening of the Hair, After Mental Strain, Arch. Neurol. & Psychiat. **24**: 415 (Aug.) 1930.

58. Landois, L.: Das plötzliche Ergrauen der Haupthaare, Virchows Arch. f. path. Anat. **35**:575-599, 1866.

59. Ornsteen, A. M.: Functional Disorders of the Nervous System as Sequelae to Trauma, Am. J. Surg. **42**:772, 1938.

60. MacLeod, J. M. H.: A Case of Leucodermia and Leucotrichia Following a Motor Accident, Brit. J. Dermat. **49**:437, 1937.

61. Roose: Cas de poliosis ou de canitie des paupiéres, Ann. Inst. Saint-Antoine (Courtrai), April 1, 1899; abstracted, Ann. d'ocul. **122**:314, 1899.

62. (*a*) de Schweinitz, G. E.: Sudden Turning Gray of the Eyelashes, M. News, Philadelphia **1**:353, 1889; Univ. M. Mag. **1**:353, 1888-1889. (*b*) Hirschberg, J.: Plötzliches Ergrauen von Haupt- (oder Bart-) Haaren, Centralbl. f. prakt. Augenh. **12**:15, 1888.

63. (*a*) Lotin, A.: Ein Fall von einseitigem Ergrauen der Wimpern bei einem Kind, Vestnik oftal., 1902; abstracted, Ztschr. f. Augenh. **10**:235, 1903. (*b*) Dayus, E. C.: Personal communication to the author. Schreiber.[51]

64. (*a*) Tay, W.: A Case of Symmetrical Whitening of the Eyelashes and Eyebrows in Connection with Sympathetic Ophthalmitis, Tr. Ophth. Soc. U. Kingdom **12**:29, 1891-1892. (*b*) Jacobi, J.: Vorzeitige und acute Entfärbung der Wimpern beschränkt auf die Lider eines sympathisch erkrankten Auges, Klin. Monatsbl. f. Augenh. **12**:153, 1874. (*c*) Nettleship, E.: Remarks on Sympathetic Ophthalmitis with Whitening of the Eyelashes, Tr. Ophth. Soc. U. Kingdom **4**:83, 1884. (*d*) Ponti, F.: Straordinario caso di precoce canizie delle ciglia, Gior. d'oftal. ital. **2**:105, 1859. (*e*) Bach, L.: Traumatische Neurose und Unfallbegutachtung, Ztschr. f. Augenh. **14**:246, 1905. Terrien.[47] Steindorff.[25e] Schreiber.[51] von Michel.[18b]

65. Gasteiger, H.: Ueber frühzeitiges Ergrauen der Cilien, Arch f. Augenh. **95**:261, 1925.

66. (*a*) Reich, M.: Péliose d'origine nerveuse, Arch. d'opht. **1**:307, 1881. (*b*) Luhr, A. F.: Personal communication to the author. Schreiber.[51] von Michel.[18b] Cramer.[14]

ness and rapidity of the change in color. Poliosis following severe emotional trauma has been termed "poliosis neurotica" by Schreiber,[51] and as astute an observer as Hutchinson[6] observed "there can be little or no doubt that these changes are brought about from lesions of the nervous system, and in that relation they are of great interest." Becker[50] asserted that the pathogenesis of poliosis is usually on a functional basis.

As previously stated, the duration of discoloration of the hair varies widely. Vogt[52] stated that in his case of this syndrome depilation of the white hair was followed by regrowth of black hair. In alopecia areata, complicated by regrowth of white hair in the affected areas, the striking piebald appearance may gradually be replaced by a more even distribution of hair pigmentation.

The not uncommon association of poliosis with either alopecia areata or vitiligo is well known. Relevant to consideration of the present case and to the hypothesis advanced is Komoto's[31a] case, in which development of chorioretinal depigmentation was associated with vitiligo and poliosis. That the associated region of the eye may be involved in sudden poliosis is suggested by the case of Roose,[61] in which the eyelashes of the right eye were reported to have turned white overnight after great fright, and by the case of Herzog, cited by Hirschberg,[62b] in which whitening of half the cilia of the right upper lid and some of the eyebrow on the same side occurred in the course of a week.

Medical, particularly dermatologic, opinion holds that poliosis may apparently be spontaneous but that in the main the pathogenesis appears to rest on a neurotropic basis. Other known or possible causes of this condition are circulatory changes, which bring about disturbance in the delivery of pigment,[64e] anaphylactic phenomena[67] and, sometimes, congenital factors.[68] Poliosis and, more commonly, alopecia have followed specific systemic bacterial disease.[52] Tay,[64a] Reich,[66a] and Hirschberg,[62b] all have stated the belief that poliosis is due to nerve influences, and the last-named author suggested that the sympathetic nervous system was involved. It is now well established that neurodermatoses involve dysfunction of the vegetative nervous system.

Poliosis is included among the functional dermatoses by various authorities. Schenkl[5] was the first, in 1873, according to Babel,[4] to observe the appearance of poliosis in association with uveitis, which in his case was of traumatic origin, evidently a true sympathetic ophthalmia. Babel did not mention the equally interesting cases reported by Hutchinson[6] and by Nettleship,[64c] in 1884. Jacobi[64b] reported a case of poliosis similar to that of Schenkl in 1874.

In another, and much earlier, paper Hutchinson[69] asked:

> Is there any reason to believe that in humans, any other nerve than the fifth can either by its irritation or its paralysis, influence the nutrition of the eyeball? Are there any facts which imply that the vaso-motor can produce any other consequences . . . ?

If, in this syndrome, the uveitis (and ocular depigmentation) are, like the alopecia, poliosis and vitiligo, secondary to disease of the hypothalamic vegetative centers, the answer to Hutchinson's question is probably "yes."

Vitiligo.—Vitiligo is a disease of the skin characterized by disappearance of the natural pigment, occurring in patches and leaving whitish areas. According to Becker and Obermayer,[39] it is immediately due to functional derangement of the melanoblasts at the epidermodermal junction. It has been reported in association with poliosis alone,[70] with alopecia,[71] with heterochromia iridis and cataract[32] and with herpes zoster ophthalmicus.[72] In the syndrome under discussion, the process usually involves the region of the brows and may occur on the scalp,[21d] trunk, limbs and genitalia. The fact that its occurrence has not been reported more consistently on the scalp may be due to the fact that the hair has masked its presence. Fluorescing ultraviolet rays bring out the presence of this lesion on the scalp in a striking manner (fig., *A* and *B*). In the case reported here the vitiligo did not appear on the scalp until late in the course of the disease, when the areas of alopecia in this region had been covered with a new growth of white hair. Photographs made with ultraviolet light also show that the vitiligo in this case did not appear simultaneously in the various areas of the skin.

Vitiligo has also been held to occur in the course of prostrating, cachectic disease.[28a] Vitiligo of the eyelids (but not of the brows) has been reported to follow local instillation of a parasympathetic drug.[73]

Although the pathogenesis of vitiligo is not entirely understood, many competent dermatolo-

67. Rones.[11] Cramer.[14]

68. Streatfield, J. F.: Observations on Some Congenital Diseases of the Eye, Lancet **1**:263, 1882.

69. Hutchinson, J.: Suggestions for Further Clinical Work in Ophthalmology, Ophth. Hosp. Rep. **8**:1, 1876.

70. MacLeod.[60] Steindorff.[25e] Becker and Obermayer.[39]

71. Becker and Obermayer.[39] Stokes, Beerman and Ingraham.[42]

72. Bauckus and others.[45] Gilbert.[30a] Erdmann.[28a]

73. Corrado, M.: Contributo alla genesi della vitiligine palpebrale consecutive ad istillazione repitute di atropina, Ann. di ottal. e clin. ocul. **60**:914, 1932.

gists regard it as a trophoneurosis or dermatoneurosis.[74] Although Demaria [75] and Gilbert [30a] stated that the vitiligo was an accidental concomitant in their cases, it is striking how completely the vitiligo in the reported cases appeared to be due to the same causes which Genner [43] and Stokes [40] listed for alopecia, viz., peripheral nerve injury, disease of the nervous system and emotional shock. For instance, Steindorff [25e] reported its occurrence after blunt trauma, and Cramer,[14] after a painful operation on the eyes; it has been described in conjunction with Horner's syndrome [76] and as following trigeminal neuralgia [63b] and reference has been made [77] to its association with herpetic states and, of course, with the syndrome under discussion. MacLeod [60] described the association of vitiligo with poliosis following severe emotional trauma. He stated: "It is significant that it [vitiligo] should first have become obvious seven weeks after the accident—a period of time when hair may begin to fall after some serious illness." Hutchinson [78] ascribed localized scleroderma (morphea) to nervous influences.

Reference has been made to the fact that this syndrome in a significant number of cases (especially significant in view of the incompleteness of many of the reports) was preceded either by an "influenzal" encephalitic prodrome or, curiously, by excruciating emotional trauma. In a few cases of this syndrome [79] the various manifestations have shown an atypical relation; their onset has been widely separated in terms of time.

REPORT OF A CASE

History.—A man aged 38, of Italian origin, born in Calabria, Italy, had been working for several months in an oil-tempering room, where steels of various types were treated. About the middle of December 1939 he observed that there were fumes in the tempering room and stated that the vapor irritated his eyes. He complained of this irritation intermittently until about March 19, 1940, when, on returning home, he told his wife that he felt cold and ill. The following day his physician diagnosed his condition as an infection of the upper respiratory tract; during the next few days the illness seemed to resemble influenza, the diagnosis which the physician made. Several days later, before convalescence was complete, the patient noted blurred vision. On the patient's complaining of impaired vision, his physician examined the eyegrounds and recognized elevation of the nerve heads. This observation was confirmed.

For several months the patient had been aware of occasional headaches. These he had attributed to the ocular irritation, which he believed was due to vapors in the room where he worked. After the onset of the infection of the upper respiratory tract the headaches became more severe and more constant and, he stated, were not relieved by medicine which his physician prescribed. He began to be annoyed by ringing in the ears. He complained of a dry, crusting discharge on the eyelids. His wife stated that the patient became lethargic and that it was on this account she became worried about him.

Inquiry into the background of the patient's health revealed nothing significant. There was no history of ocular disease in the family, but examination of his wife revealed an advanced degree of retinitis pigmentosa in each eye.

The patient was admitted to the Buffalo General Hospital on March 29, at the request of the attending physician. There was no elevation in temperature or in the pulse or the respiratory rate. On admission the bulbar conjunctiva of each eye was injected; the ocular media were clear, and there was bilateral papillitis. Physical examination revealed nothing abnormal except for deviation of the nasal septum and pyorrhea.

Laboratory Data.—March 29: Repeated urinalyses revealed nothing except a few white blood cells.

A blood count showed 5,620,000 red cells, a hemoglobin concentration of 113 per cent and 4,450 white cells, with 17 band forms, 71 filiform neutrophils and 12 lymphocytes. A week later the white cell count was 7,600, with 14 band forms, 59 filiform neutrophils, 3 eosinophils, 18 lymphocytes and 6 monocytes. On two occasions the Wassermann reaction of the blood was negative. The dextrose of the blood measured 111 mg.; the urea nitrogen, 13 mg., and the sodium chloride, 467 mg. per hundred cubic centimeters. The sedimentation rates were normal. Bacteriologic examination of a smear of dental material showed fusiform bacilli and spirilla.

April 4: The spinal fluid was clear and colorless; it contained 3 red blood cells and 343 white blood cells per cubic millimeter, with lymphocytes predominating; the reaction for globulin was 1 plus, and that for albumin, 2 plus; there was prompt reduction of copper; the colloidal gold curve was 2222110000. The Wassermann reaction was negative. The protein measured 58 mg., and the chlorides 660 mg., per hundred cubic centimeters.

April 9: The spinal fluid was clear and colorless. Examination revealed 333 white blood cells per cubic millimeter, with lymphocytes predominating, and a trace of albumin and globulin; there was delayed reduction of copper. The protein measured 59 mg., and the dextrose 49 mg., per hundred cubic centimeters. Culture of the fluid yielded Bacillus subtilis; a smear showed no acid-fast bacilli.

April 16: The spinal fluid was clear and colorless. Examination revealed 3 red blood cells and 122 white blood cells, with lymphocytes predominating; a plus-minus reaction was obtained for globulin and a plus reaction for albumin; there was a prompt reduction of

74. Erdmann.[28a] McCarthy.[38] Stokes.[40] Stokes, Beerman and Ingraham.[42]

75. Demaria, E. B.: Consideraciones sobre dos casos de iridociclo-coroiditis doble y grave, en sujetos con vitiligo, Arch. de oftal. hispano-am. **17**:355, 1917.

76. Jonesco-Sisesti; Vasilesco, N., and Palade, G.: Sclérose en plaques avec syndrome de Claude Bernard-Horner et vitiligo, Bull. et mém. Soc. méd. d. hôp. de Paris **53**:941, 1937.

77. Baldino, S.: Irido-coroidite di origine endocrino-simpatica, Arch. di ottal. **27**:244, 1920. Gilbert.[30a] Bauckus and associates.[45]

78. Hutchinson, J.: On Structural Diseases Induced Through the Influence of the Nervous System, Brit. M. J. **2**:915, 1880; Lectures on Clinical Surgery, London, J. & A. Churchill, 1879, p. 338.

79. Babel.[4] Gilbert.[30a] Wexler.[31b] Corrado.[73]

copper, and the colloidal curve was 1111110000; the Wassermann reaction was negative, and the protein measured 150 mg. per hundred cubic centimeters.

April 22: The spinal fluid was slightly cloudy. Examination revealed 21 white blood cells and no red cells, with polymorphonuclear cells predominating. There were a slight trace of globulin and albumin and prompt reduction of copper. The dextrose content was 55 mg. per hundred cubic centimeters. There were no acid-fast bacilli, and inoculation of a guinea pig gave negative results for tuberculosis.

Course of Illness. — Roentgenographic examination during the course of hospitalization showed that the nasal sinuses, gums and teeth were essentially normal, and encephalographic studies gave good visualization of the ventricular system, which appeared to be normal. Continued observation of the fundi revealed, in addition to the bilateral papillitis previously observed, some retinal edema.

On April 13, the clinical impression was that of meningeal reaction, and one neurologic consultant recorded slight paresis of the right sixth nerve. The following day a neurologic consultant gave it as his opinion that there was an inflammatory lesion primarily of the optic nerve and secondarily of the meninges. Gradually the media became more hazy, and anterior uveitis developed in each eye.

I first saw the patient on June 1, 1940, about two months after the onset of the disease. He stated that about six weeks after the beginning of the loss of vision, he became aware of considerable loss of hair on the scalp. For several weeks, he stated, he found

Fig. 1.—Photographs of patient (*A*) on July 1, 1940, showing alopecia and developing vitiligo, and (*B*) on Dec. 23, 1940, showing vitiligo and poliosis. Ultraviolet illumination. (*C*) photograph of patient on Dec. 23, 1940, with ordinary incandescent illumination. The vitiligo is less clearly demonstrated than with ultraviolet illumination.

a good deal of hair on his pillow in the morning. At this time, he said, his brows and lashes began to turn white (fig. 1*A*).

He also complained of partial loss of hearing and of persistent ringing in the ears. He stated that during the first few days of his hospitalization he had a severe headache, which was not relieved at all by medication, and that tinnitus began at that time. During his stay in the hospital, the tinnitus became much less noticeable in the left ear and finally disappeared on that side. He was certain that the headaches and the tinnitus on the left side had stopped three weeks before he left the hospital, on May 20.

Examination.—The patient was well developed. Both eyes showed a moderate degree of injection of the conjunctiva and deep ciliary area. Extraocular muscle balance was normal. Vision in each eye was reduced to light perception and was not improved with glasses. Many keratitic precipitates were dispersed over the entire posterior surface of both corneas. In the left eye the anterior chamber was slightly shallow, the aqueous clear and the margin of the iris entirely adherent to the lens, while in the right eye seclusion of the pupil was nearly, but not quite, complete. The irises were brown and showed some degree of atrophy but no areas of depigmentation. Light projection was present in all directions in both eyes. There was no abnormal interference with transillumination; in fact, transscleral illumination showed pronounced atrophy of the pigment coats of the eyes, with normal density remaining in the region of the ciliary body. There was no corneal hypesthesia. Intraocular tension was 17 mm. (Schiøtz), and in each eye there was a slight degree of tenderness in the ciliary region. The upper and lower lashes of each eye showed partial canities, as did the eyebrows. The skin in the region of the brows showed a clearly delimited loss of pigment. These vitiliginous areas fluoresced rather brilliantly in ultraviolet light, as did several irregular depigmented areas on the skin of the back. Aside from a faint erythema of the margins, there was no sign or evidence of inflammation in or about these areas of leukoderma. The hair of the scalp showed conspicuous patchy areas of baldness, typical of alopecia areata, and these same areas were vitiliginous.

The alopecia also involved the eyebrows and eyelashes, while some of the areas of alopecia on the scalp were completely devoid of hair. Others showed regrowth. The new hairs were somewhat finer and were white. The alopecia of the eyebrows and eyelids was diffuse and not complete. The scalp, the eyebrows and the eyelids showed a diffuse, desquamating, fine dry scale, which had a bright fluorescence with ultraviolet illumination. This scaling was undoubtedly a manifestation of seborrhea. The vitiliginous areas on the back were chiefly in the region of the third and fourth thoracic vertebrae, and there was a faint erythema of the margins. There was no evidence of any inflammatory reaction in this area of leukoderma. None of the lesions were elevated or depressed. Direct microscopic examination and cultures on the Sabouraud medium of scrapings taken from the patches of alopecia and the areas of vitiligo did not reveal the presence of fungi.

On observation with ultraviolet light the vitiligo was much more perceptible. Examination of the nose and throat gave essentially negative results. The ear drums and auditory canals were normal, the eustachian tubes patent and the sinuses clear on transillumination, except for the right antrum, which was clear after irrigation. Audiometric, Weber and caloric tests showed eighth nerve deafness on both sides, not sufficient to destroy all hearing, with functioning labyrinths.

Electroencephalograms did not disclose abnormal potentials. The basal metabolic rate was + 1 per cent.

Progress of the Disease and Present Status.—Progressive changes were limited to the skin, the vitiliginous areas of which showed gradual extension and in which, on the scrotum, violaceous, flat-topped, shiny papules developed, diagnosed as lichen planus; to the hair, with regrowth of white hair in the regions of baldness, producing a striking piebald appearance, and to the eyes, in which the keratitic precipitates became heavier. Later, in October 1942, wheal-like, large papules and bullous lesions developed on the forearms and neck and about the lips; these lesions were diagnosed clinically as erythema multiforme. The tinnitus has persisted "in the right ear." The audiogram taken a year after the first examination showed no change in the partial deafness. Neurologic examinations have revealed nothing significant, although in January 1941 the patient complained of formication, "as though a feather were touching the skin of the head"; by this, he referred to the skin on each side of the head around and above the ears and extending forward to the region of the orbit. This disturbance persisted about ten days. He stated that, beginning about three months after the onset of the illness, he drank more water than previously and that nocturia appeared, micturition averaging once a night. He has noted no change in his appetite for food or loss of libido. There has been no loss of weight.

After operation on the eyes a dense secondary membrane developed in each eye. Iridotomy on the left eye improved vision, with correction, to 20/70 in that eye. No further surgical intervention was attempted on the right eye. The patient has returned to his former occupation. No secondary glaucoma has developed. On the contrary, since operation there has been a varying degree of hypotonicity in the right eye; otherwise it has been quiet and comfortable. At no time has there been evidence of retinal detachment in either eye. Transscleral transillumination shows atrophy of the pigment layers of the eyes, which is now pronounced.

Inoculation Studies.—Using a technic demonstrated to me by Dr. P. K. Olitsky and Dr. Helen Morgan, at the Rockefeller Institute, I gave 4 rabbits intracisternal injections of material from the iris of the right eye, macerated in sterile isotonic solution of sodium chloride. All the rabbits survived. Over a period of six months no organic changes were observed. Three rabbits received similar injections of material from the left eye. Again, no changes were noticed in the skin or the pigmentation of the hair. Two rabbits were killed and sent to Dr. James Papez for examination of the midbrain.

The negative results obtained with animal inoculation at this stage demonstrate the importance of obtaining potentially infected tissue early in the disease, perhaps when the cell count of the spinal fluid is high. It is suggested that cerebrospinal fluid might be used for injection. I should be pleased to cooperate with investigators who have cases of this rare disease under observation and who are not familiar with the rather difficult technic of intracisternal injection into the rabbit.

HYPOTHALAMUS

Anatomic Structure.—The hypothalamus is a name applied to the mamillary bodies, the tuber cinereum and other related structures between the cerebral peduncles and the subthalamic region,[80] which form the floor of the third ventricle. Largely composed of nuclear masses and their tract connections, it is situated just above the hypophysis, below the thalamus and just behind the optic chiasm. Knowledge of the anatomic divisions, the cytoarchitecture, the tract connections and the highly organized, largely vegetative, functions which it integrates is recent for the most part, although Mauthner, an ophthalmologist, ascribed the somnolence associated with encephalitis to an infection of the brain,[81] described engorgement of the walls of the third ventricle and the sylvian aqueduct and, accordingly, conceived of a center for sleep regulation in the hypothalamus. Lesions, such as tumor, in the hypothalamic region produce symptoms simulating those of encephalitis.[82] The patient whose case is reported here appears to have had encephalitis, indicating hypothalamic involvement early in the disease.

The hypothalamic nuclei are numerous, numbering at least fifteen.[81a] To many no specific function has been assigned.[81a] Although commendable attempts have been made [83] to systematize the confusing nomenclature of hypothalamic structure, morphologic relevance in this area is obscure; there appears to be reason to believe that classification of nuclei on the basis of cell type is more illuminating in this area than that based on topographic arrangement.[84]

Embryologically the retina is closely connected with the hypothalamus and the third ventricle.[85] The optic stalks are joined to the part of the first primary cerebral vesicle, from which the hypothalamus is later derived. As Haymaker and his associates [86] pointed out, this relation serves as a clue to the association of pigment changes in the retina with, and he presumed hypothalamic changes in, the Laurence-Moon-Biedl syndrome.

Papez [87] succinctly summarized the close phylogenetic and embryonic relations of the retina, hypothalamus and hypophysis. He made it clear that the apparent complexities of the hypothalamus and its activities can be understood best when considered from the aspect of the numerous structural connections of the region and in the light of its development. While the growth of the hypothalamus is not a uniform, but a differential, process, the development of the optic tracts and the supraoptic decussations seems to be closely related to the origin and growth of the supraoptic nucleus and the anterior hypothalamic area. The development of fibers from the latter and from the supraoptic region occurs early. This fact points to the importance of the hypothalamohypophsial connections, to which I shall refer.

The most anterior portion of the hypothalamus contains the supraoptic, paraventricular and suprachiasmic nuclei, which are connected by fiber tracts with various parts of the hypothalamus, and notably with the hypophysis, the retina and the thalamus. Many of the details of the fiber connections of the hypothalamus have not been worked out; only in recent years [81a] have certain hypothalamic functions been intensively studied, especially in regard to sleep rhythm, control of sympathetic and parasympathetic activity, heat regulation; water, carbohydrate and fat metabolism and sexual pressures.

The evidence that fiber tracts connect the retina and the hypothalamus is now convincing. Haymaker [88] showed, in the dog, a discrete bundle of fibers in the upper lateral part of the optic nerve, slipping away from the optic chiasm and extending to the supraoptic nucleus. Papez [82] has shown me a similar structure in serial sections, an observation which Haymaker [88] regarded as authoritative. Frey [89] claimed to have shown a similar structure in the guinea pig, but

80. Papez, J. W.: Comparative Neurology, New York, Thomas Y. Crowell Company, 1929, p. 297.

81. (*a*) Fulton, J. F.: Physiology of the Nervous System, New York, Oxford University Press, 1938, pp. 223-253. (*b*) Lebensohn, J. E.: The Eye and Sleep, Arch. Ophth. **25**:401 (March) 1941.

82. Papez, J. W.: Personal communication to the author.

83. (*a*) Clark, W. E. L.; Beattie, J.; Riddoch, G., and Dott, N. M.: The Hypothalamus, Edinburgh, Oliver & Boyd, Ltd., 1938. (*b*) Rioch, D. M.; Wislocki, G. B., and O'Leary, J. L.: A Précis of Preoptic, Hypothalamic and Hypophysial Terminology with Atlas, A. Research Nerv. & Ment. Dis., Proc. (1939) **20**:3, 1940.

84. Morgan, L. O.: Cell Changes in Hypothalamus in the Major Psychoses, A. Research Nerv. & Ment. Dis., Proc. (1939) **20**:753, 1940.

85. Ryder, J. A.: Development of the Eye, in Norris, W. F., and Oliver, C. A.: System of Diseases of the Eye, Philadelphia, J. B. Lippincott Company, 1897.

86. (*a*) Haymaker, W., and Saunders, J. B. de C. M.: Hypothalamus: Present Conception, Internat. Clin. **2**: 226, 1940. (*b*) Haymaker, W., and Anderson, E.: Hypothalamus: Functions and Clinical Syndromes of the Hypothalamus, ibid. **2**:253, 1940.

87. Papez, J. W.: The Embryologic Development of the Hypothalamic Area in Mammals, A. Research Nerv. & Ment. Dis., Proc. (1939) **20**:31, 1940.

88. Haymaker, W.: Personal communication to the author.

89. Frey, E.: Studien über die hypothalamische Optikuswurzel der Amphibien, Proc. Sect. Sc. Roy. Acad. Sc., Amsterdam **41**:1004, 1938.

it is possible that he saw only aberrent fibers of the optic decussation.

As early as 1931, Greving,[90] whose anatomic description of the hypothalamic nuclei Fulton found most satisfactory, observed in the human brain a contingent of fibers escaping from the optic chiasm (derived presumably from the retina), to enter the hypothalamus and pervade the supraoptic nucleus. These retinal-hypothalamic connections are not to be regarded [88] as identical with aberrent fibers of the optic decussation, described by Jefferson [91] in the ferret. According to Frey,[92] the hypothalamic root of the optic nerve is highly developed in man. Marburg [93] corroborated this statement.

Similarly, the existence is now accepted [94] of hypothalamohypophysial fibers, functionally related to retinal-hypothalamic tracts and forming with them (to view the matter simply) retinal-hypophysial connections. The same supraoptic nucleus previously referred to as the terminus of the retinal fibers gives rise [81a] to the supraopticohypophysial tract, which terminates in the pars intermedia and the pars posterior of the pituitary. Other hypothalamohypophysial connections are said to involve the paraventricular nucleus, of the hypothalamus,[81a] the median eminence and the pars tuberalis, of the pituitary. Diencephalohypophysial connections were described in the fish by Ariëns Kappers [95] as early as 1906, and the evidence for the existence of similar tracts in other species was reviewed by Scharrer,[94] Haymaker and Saunders [86] and Clark and associates.[83a]

Functional Evidence of Retinohypothalamohypophysial Relations.—It is well known that the melanophore hormone of the pituitary will cause "pigment migration," or expansion of the melanophores, in the skin of the frog, which becomes dark. Frogs without a hypophysis do not change color, as do normal frogs when moved from a light to a dark room, or vice versa. Furthermore, no melanophore hormone is found in the hypophysial extract of the frog killed after it has remained in darkness twenty minutes; but if the donor frog is allowed to remain a few seconds in daylight, light stimuli from the eye activate the hypophysis, and an extract prepared from its hypophysis will produce darkening of the skin of the frog given the injection. It has also been shown [96] that the melanophore hormone is increased in the blood stream of human subjects and of rabbits during the night.

That there is a remarkably close functional association of the hypothalamus and the hypophysis is indicated by the experiments of Cushing and Clark and associates,[83a] showing that hypothalamic function is stimulated by a pituitary secretion, which may be carried to the hypothalamus not only by the blood stream but by a hypophysial colloid secreted directly into the third ventricle, adjacent to the hypothalamus. The embryonic relations of the anterior hypothalamus, hypophysis, retina, optic tracts and supraoptic decussations (including Gudden's commissure) have been previously indicated.[87] Functionally there is a relation of the retina, via the optic tracts, the hypothalamus and the activity of the pituitary, as shown by experimental work on amphibians,[89] hens [97] and other vertebrates.[98]

There is much evidence to indicate that gonadal activity and genital development are influenced when the optic nerve is stimulated. It is widely known that egg production is increased when the hen house is illuminated at night; equally effective is pinching the optic nerve.[91] Rodewald [99] showed that visual or mechanical stimulation affected the testicular structure of male ducks, and this relation of retinal to pituitary activity has been confirmed by the work of other investigators and reviewed recently by Haymaker and Saunders,[86] whose attention it has not escaped that light is effective in stimulating gonadal activity in wild animals and in man. The effect of the light stimulus on sexual cycles and on dermatoneuroses, as well as on basic ethnologic factors, was reviewed in 1916 by Woodruff in a comprehensive monograph.[100] More re-

90. Greving, R.: Die vegetative Zentren im Swischenhirn, in Müller, L. R.: Lebensnerven und Lebenstriefe, Berlin, Julius Springer, 1931, p. 115.

91. Jefferson, J. W.: A Study of the Subcortical Connections of the Optic Tract System of the Ferret, with Special Reference to Gonadal Activation by Retinal Stimulation, J. Anat. **75**:106, 1940.

92. Frey, E.: Vergleichend-anatomische Untersuchungen über die basale optische Würzel, usw., Schweiz. Arch. f. Neurol. u. Psychiat. **39**:255, 1937.

93. Marburg, O.: Personal communication to the author.

94. Scharrer, E.: Ueber ein Vegetatives optisches System, Klin. Wchnschr. **16**:1521, 1937. Lebensohn.[81b] Haymaker.[88]

95. Ariëns Kappers, C. U.: The Structure of the Teleostan and Selachian Brain, J. Comp. Neurol. **16**:1, 1906.

96. Jores, A.: Melanophorenhormon und Auge, Klin. Wchnschr. **12**:1599, 1933; cited by Scharrer.[94] Greving.[90]

97. Morgan, L. O.: Personal communication to the author.

98. Clark, W. E. L.; McKeown, T., and Zuckerman, S.: Visual Pathways Concerned in Gonadal Stimulation in Ferrets, Proc. Roy. Soc., London, s.B **126**:449, 1939.

99. Rodewald, W.: Die Wirkung des Lichtes auf die Hypophyse von Rana tempororia L., Ztschr. f. Vergl. Physiol. **21**:767, 1935; cited by Scharrer.[94]

100. Woodruff, C. E.: The Effects of Tropical Light on White Men, New York, Rebman Company, 1916.

cently, Sanchez-Calvo [101] has shown that rabbits and guinea pigs exposed to darkness for as short a period as three days show cellular changes in the hypophysis. In man, also, sexual activity is affected by stimulation with light. As Haymaker and associates [86] pointed out, it is generally recognized that the people of a southern climate reach sexual maturity earlier than do northern races. Llewellyn [102] stated that during the long polar night, Eskimo women neither menstruate nor conceive, and Woodruff [100] stated that the return of spring brings what really amounts to a rutting season among these people. There is a good deal of evidence to support the contention that light, rather than other climatic factors, principally affects the sexual cycles in mammals. Much of the evidence was summarized by Woodruff,[100] who also stated that light influences the fattening of cattle (and of human beings). It will be recalled that fat metabolism is influenced by the hypothalamus.

Many investigators have used the technics of ablation, tract section and excitation to study hypothalamic activity in general, including the role which visual impulses play in gonadal activity. Ablation and tract section technics do not allow close comparison with the more subtle effects, involving both depression and excitation of function, which are presumably produced by the hypothalamic lesions of disease. The defects of excitation technics have been analyzed by Fulton.[81a] Recently the view was expressed [103] that visually generated impulses pass via the optic pathway and the supraoptic and tuberal nuclei of the hypothalamus, and thence via the supraopticohypophysial and tuberohypophysial tracts of the anterior lobe of the hypophysis, or to the pars intermedia and the pars posterior.[81a] Haymaker [88] also stated:

> Another possible reflex pathway from retina to hypophysis is via accessory optic tracts to the subthalamus and thence via the fasciculus tuberis descendens to the tuber cinereum, where a relay enters the neurohypophysis.

Roussy and Mosinger [104] stated that hypothalamosensory fibers include retinal connections which can be demonstrated in man—that these fibers probably regulate the excitability of the retina (the question of cerebral influences on dark adaptation arises) and may supply trophic innervation to the retina and choroid. They suggested that these connections explain structurally the relative frequency (referred to from the embryologic standpoint in a preceding paragraph with which retinosis pigmentosa is associated with hypothalamic lesions, e. g., the Laurence-Moon-Biedl syndrome.

A considered opinion probably will hold [105] that it is all too easy, on the basis of theoretic consideration, to ascribe unprovable functions to tenuously defined tracts in the hypothalamus, to diencephalic nuclei which are topographically diffuse and possibly more easily classified in terms of cell type. It is probably well to remember that, as Clark stated, the hypothalamus is phylogenetically one of the most ancient parts of the vertebrate forebrain; and it may well be, as Riley suggested, that even some of the tracts discernible in man are vestigial and of little functional importance. But the fact that the hypothalamus does show alteration in cases of various systemic diseases in which there has been opportunity to examine it [84] and that the morbid processes known to involve the hypothalamus, as well as experimental lesions in this area, cause a wide variety of systemic manifestations serve to emphasize the exceedingly active role the hypothalamus plays in the hierarchy of the vegetative nervous system.

Justification for my proposing the hypothesis presented in this paper, without, at present, much substantiation based on human material or animal experimentation, may be found in the following facts:

1. The disease is rare, and unless the greatest possible utilization is made of all human material as it becomes available, answers to these important questions may long be postponed.

2. The disease is obviously not one that lends itself readily to experimentation on living human subjects.

3. There is reason to believe that it may be possible to transmit the causative agent of the disease, presumably a virus, to certain experimental animals. Such transmission is not easily accomplished, in view of the rarity of the disease, and since the infective material must be obtained from the spinal canal or from intraocular tissue of infected subjects, the need to conserve the small amount of tissue available for this purpose is readily apparent.

101. Sanchez-Calvo, R.: Einfluss der Dunkelheit auf das Zellbild der Hypophyse, Virchows Arch. f. path. Anat. **300**:560, 1937.

102. Llewellyn, L. J.: Light and Sexual Periodicity, Nature, London **129**:868, 1932.

103. Cahane, M., and Cahane, T.: Sur certaines modifications de l'hypophyse après une lésion du centre infundibulaire régulateur de la function génitale, Rev. franç. d'endocrinol. **13**:366, 1935; Sur certaines modifications des glandes endocrines après une lésion diencephalique, ibid. **14**:472, 1936; cited by Haymaker and Anderson.[86b]

104. Roussy, G., and Mosinger, M.: L'hypothalamus chez l'homme et chez le chien, Rev. neurol. **63**:1, 1935.

105. Riley, H. A.: Epidemic Encephalitis, Arch. Neurol. & Psychiat. **24**:574 (Sept.) 1930. Penfield, W.: Diencephalic Autonomic Epilepsy, Arch. Neurol. & Psychiat. **22**:358 (Aug.) 1929.

Shortly after the patient whose case is reported here came under my observation, it occurred to me that there might be some way of accounting for the bizarre and striking manifestations of this syndrome in terms of a discrete lesion. It would be surprising if a case of this sort did not incite speculation regarding the pathogenesis of the syndrome. The rather definite encephalitic prodrome must suggest a basal intracranial lesion; and consideration of the material reviewed in the fields of morphologic and functional neurology, and of certain provocative concepts in neurodermatology advanced by Stokes, Beerman and Ingraham,[42] leads me directly to the conclusion that a lesion in the suprachiasmatic region of the hypothalamus, and only that one lesion, would account for the entire syndrome, including prodromal encephalitis (usually present), uveitis, certain dermatoneuroses, dysacousia and, sometimes, pronounced cryesthesia. I brought the matter before Dr. James Papez, who corroborated my suggestion and put me into touch with recent authoritative work in this field.

Heersema [106] stated that the symptoms of initial encephalitis include headache, mild fever and general malaise, somnolence or disturbance in sleep rhythm, visual disturbances, choreiform movements, and even paralytic symptoms of the extremities. It is well known that these features may subside on recovery of the patient from the acute stage, and it may be difficult to obtain a significant history when one is attempting to establish evidence to explain the appearance of encephalitic sequelae months or years later, especially in the absence of any epidemic.

Fulton [81a] quoted, and apparently accepted, the statement of von Economo [107] and that of Eaves and Croll [108] that the hypothalamus is invariably involved in encephalitis lethargica. In this disease the disturbance of sleep rhythm is referred by most authorities to the hypothalamus.[80] This symptom was pronounced in the present case, as in other cases of the syndrome under discussion. The cryesthesia mentioned in the reports of several cases of the syndrome also points to this region of the brain.[109] Dott and associates [83a] cited a case in which a man with a large intrasellar cyst became subject to hot sweats and sensitive to cold and constantly felt so cold that he wore socks and required hot water bottles in bed, even in warm weather. This case bears a striking similarity to that of a patient with the syndrome of oculocutaneous pigmentosis, reported by Avalos,[21d] who experienced severe cryesthesia. The fact that the thermal disturbances were largely subjective, as far as one can tell from the reports, suggests that tracts known to connect the hypothalamus with the thalamus,[110] or the thalamus itself, may have been involved.

Hyperglycemia, reported in 1 case of this syndrome,[24] was attributed by the observer to hypophysial derangement. The hypocholesteremia in the same case might fit in with the concept of a hypothalamic lesion, since there is sufficient reason to believe that the role of the hypothalamus in the regulation of fat metabolism is closely associated with its influence on the metabolism of carbohydrates.[81a]

Although the comprehensive reviews of hypothalmic correlations of Grinker, Ingram and Ranson,[111] and the definitive monograph of Clark and associates [83a] on the hypothalamus do not mention a single cutaneous expression of disturbance of this region, Stokes [40] was impressed by reports of "extraordinary seborrheic activity with accompanying dermatitis observed in cases of encephalitis." It is conceivable, Papez [82] agreed, that fibers from the supraoptic region to the pars intermedia of the hypophysis may mediate the alopecia areata, poliosis and vitiligo observed in this syndrome. Morgan [97] concurred in this opinion; he expressed the belief that the changes in pigment in the pigmentary layer of the eye and in the skin may be ascribed to a lesion in the suprachiasmic gray matter of the hypothalamus. Marburg [93] would seem to agree; he found that hypothalamic influence on sudden change in color in lower animals is direct but that hormonal and vegetative mechanism are involved in the more highly developed organisms. The role which the hypothalamus plays in organic disturbances precipitated by dysfunction of the vegetative nervous system, as Fulton pointed out,[81a] was not recognized until attention was recently focused on the possibility that such

106. Heersema, P. H.: Symposium on Present State of Endocrine Therapy, M. Clin. North America, 1940, p. 1181.

107. von Economo, C.: Encephalitis Lethargica: Its Sequelae and Treatment, translated by K. O. Newman, New York, Oxford University Press, 1931.

108. Eaves, E. D., and Croll, M. M.: Pituitary and Hypothalamic Region in Chronic Epidemic Encephalitis, Brain **53**:56, 1930.

109. Ziegler, L. H., and Cash, P. T.: A Study of the Influence of Emotions and Affects on the Surface Temperature of the Human Body, Am. J. Psychiat. **95**:677, 1938. Fulton.[81a]

110. Rioch, D. M.: Studies on the Diencephalon of Carnivore: III. Certain Myelinated-Fibre Connections of the Diencephalon of the Dog, Cat, and Aevisa, J. Comp. Neurol. **53**:319, 1931.

111. Grinker, R. R.: Hypothalamic Functions in Psychosomatic Interrelations, Psychosom. Med. **1**:19, 1939. Ingram, W. R.: The Hypothalamus: A Review of the Experimental Data, ibid. **1**:48, 1939. Ranson, S. W.: Note with Regard to Temperature Regulation, ibid. **1**:92, 1939.

changes might involve hypothalamic centers, and the necessary tissue studies were carried out. He referred specifically to the effects of hypothalamic lesions on the gastrointestinal tract. In cases of pellagra, in which dermal manifestations, including pigmentation, are characteristic, degenerative changes have been described in the hypothalamic nuclei, and Vonderahe,[21g] who tentatively accepted these reports, called attention in this connection to Rassulev's [112] observation that about 25 per cent of the patients with pellagra present symptoms of mild diabetes insipidus, the causative lesion of which is known to involve primarily the supraoptic nuclei.

That a lesion in this area of the hypothalamus may cause alopecia, poliosis and vitiligo is evidenced by the case reported by Vonderahe and Abrams [113] of a man aged 40; there were, in addition to evidence of an expanding intracranial lesion, definite changes in the color of the skin, especially around the eyes, alopecia and rapid graying of the hair of the head, as well as nocturia and polyuria. It is now well established that the hypothalamus controls water metabolism and that diabetes insipidus is essentially a hypothalamic derangement, involving especially [83a] the supraoptic nucleus previously referred to. Their patient complained of impotence, which is, as Riddoch [83a] stated, a hypothalamic symptom. In this case, too, as in most of the reported cases of the syndrome under discussion, there was dysacousia, which consisted of buzzing and ringing in the ears and definite impairment of hearing in the left ear. The skin changed color (darkened), especially around the eyes. There was an increasing tendency toward lethargy. Autopsy showed an ependymoma of the third ventricle, distending especially its left wall, impinging on the hypothalamus and destroying the mamillary bodies. The fiber pathways in the corpus callosum immediately superior to the third ventricle presented extensive degenerative changes, evidently an effect of pressure. The columns of the fornix in the roof of the third ventricle were similarly affected. There was notable loss of cells in the thalamus. The fiber tracts of the internal capsule on each side showed loss of myelin. The anterior commissure was involved by the tumor. The globus pallidus showed loss of cells. The optic chiasm was directly invaded by the tumor. The tuber cinereum was completely replaced by neoplastic growth.

Plummer and Jaeger [114] described pigment changes in a young man in whom a glioblastoma had invaded the tuber cinereum and the right hypothalamic region. He was dark of complexion; but his skin grew lighter, and the hair of the beard, lashes, brows and axillary and pubic regions became first lighter and then sparse. Polyuria and fatigability were noted.

Laje Weskamp [19] attributed the dysacousia in his case of the syndrome to disturbance of the vegetative nervous system, specifically of the carotid plexus or the petrous nerve. It is held [82] that the supraoptic decussation of Gudden carries fibers connecting the dorsal anterior parts of the medial geniculate bodies. Clark and his associates [83a] stated that fibers in Gudden's commissure can be traced on each side back to the medial geniculate bodies and that it is possible that some fibers extend to the inferior colliculus (quadrigeminal body), and perhaps to the nucleus of the lateral lemniscus. One may conclude that this commissure is an integral part of the auditory system of the forebrain. Involvement of this structure in pathologic processes affecting adjacent areas might account for the dysacousia both in cases of this syndrome and in the case of Vonderahe and Abrahams [113] (see also the case of Hamby and Gardner [115] of ependymal cysts with bilateral deafness and figure 2).

There remains only the question of the possible relation of a hypothalamic lesion to the uveitis. Evidence is ample that retinohypothalamic nerve tracts exist in man,[93] as well as in animals.[94] On the basis of investigations with experimental animals, largely in the field of animal husbandry, it appears probable that at least some of these fibers are afferent; but, as has previously been pointed out, Roussy and Mosinger [104] described an efferent pathway to the retina, from the tangential nucleus (nucleus supraopticus), which probably regulates the excitability of the retina and possibly supplies trophic innervation to the retina and the choroid. They suggested that this trophic innervation may exert a controlling influence on deposition of the retinal pigment, and in this way explain the relative frequency of the association of retinal pigmentation with a disease in which hypothalamic involvement is suspected, namely, the Laurence-Moon-Biedl syndrome.

There is also reason to believe that a pathway exists not only from the retina to the supra-

112. Rassulev, J. A.: Ueber Diabetes insipidus bei Pellagra, Arch. f. Schiffs- u. Tropen- Hyg. **36**:481, 1932.

113. Vonderahe, A. R., and Abrams, N. R.: Ependymoma of the Third Ventricle, Arch. Ophth. **12**:693 (Nov.) 1934.

114. Plummer, D. E., and Jaeger, J. R.: Pituitary Cachexia (Simmond's Disease): Report of a Case with Autopsy, Arch. Neurol. & Psychiat. **40**:1013 (Nov.) 1938.

115. Hamby, W. B., and Gardner, W. J.: An Ependymal Cyst in the Quadrigeminal Region, Arch. Ophth. **57**:393, 1928.

chiasmic nucleus but thence, by way of the infundibulum, to the pituitary,[116] and it appears possible that pigmentary changes in the eyes, as well as in the skin and hair, may have their pathogenesis in the suprachiasmic gray matter of the hypothalamus. As early as 1911 Erdmann [28a] commented on the association of dermal vitiligo with depigmentation of the ocular fundus and suggested that depigmentation of the retina, or of the iris, may in a sense be a trophic neurosis. He also pointed out the relation of "ocular vitiligo" to herpetic disease and asserted that vitiligo and uveitis may have a common origin. Since herpetic disease of the eye is certainly due to virus infection, discussion, later, of the probable virus nature of this syndrome is justified. Baldino [77] described a case of vitiligo of the skin, the eyelids and the iris, following herpetic iritis, and Gilbert [30a] stated that depigmentation of the ocular fundus and that of the skin and hair are comparable. In cases of this syndrome, when

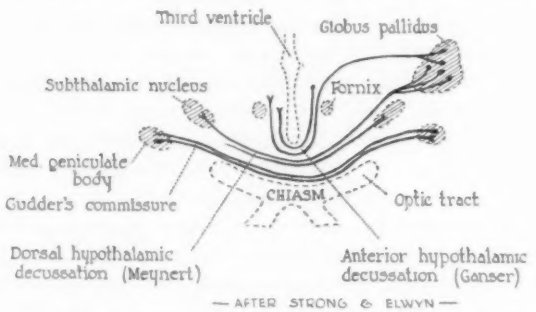

Fig. 2.—Relations of the commissure of Gudden (after Bailey, F. R.; Elwyn, A., and Strong, O. S.: Bailey's Text Book of Histology, ed. 9, Baltimore, William Wood & Company, 1936).

opacification of the media has not obscured the fundus, a striking depigmentation has been observed [31a,b]

Komoto [31a] was the first to describe vitiligo of the fundus as a part of the syndrome. He noted that the poliosis and dermal vitiligo occurred at about the same time and suggested that the absorption of pigment in the two structures had a common cause. Whatever may be the nervous mechanism involved in all the pigment changes in this disease, it is probable that they are closely related. It is well known that the pars intermedia of the hypophysis exerts control of pigmentation in the body, and to me it seems possible that a lesion involving the fiber tract from the supraoptic region to the hypophysis produces the alopecia areata, the poliosis and the dermal vitiligo and that the profound disturbances of the pigment structures in the eye may be responsible for the severe inflammatory process which follows, somewhat as a melanotic sarcoma of the choroid may produce intraocular inflammation, even that closely resembling, if not identical with, sympathetic ophthalmia.

The reasons for the belief that the hypothalamus is implicated in this syndrome may be summarized as follows:

1. Clinical evidence presented by this syndrome of oculocutaneous pigmentosis points to early involvement of the hypothalamus.

2. The posterior segment of the eyeball is closely related structurally, embryologically and phylogenetically to the hypothalamus.

3. Functional considerations point to retinohypothalamic relations.

4. A lesion in the region of the supraoptic-suprachiasmic nuclei of the hypothalamus would, in a very small area, involve or impinge on centers and tracts which, on the basis of considerable evidence, control or affect pigmentation of the eyes, hair and skin, as well as hearing.

5. Hypothalamic involvement accounts for the lethargy and cryesthesia which some of these patients experience.

6. Only one lesion, and that in the suprachiasmic region, can account for all the symptoms of this syndrome.[108]

In summary, then, it may be said that anatomic and physiologic facts substantiate the existence of a vegetative optic system and that the evidence does not conclusively demonstrate that all the fibers are strictly afferent. The existence of these tracts, in fact, recalls a question which, in 1876, Jonathan Hutchinson [69] asked future investigators to consider: "Is there any reason to believe that in humans, any other nerve than the fifth can, either by its irritation or its paralysis, influence the nutrition of the eyeball?" Does it appear less credible that pronounced changes in pigment deposit in the eye may be subject to control by the autonomic nerve system than that such nerve control exists with respect to the skin and hair? The evidence that poliosis and vitiligo are dermatoneuroses has been shown to be more than suggestive. The pronounced "whitening" of the ocular fundus in cases of Harada's disease.[31b] and in certain cases of this syndrome points to such a parallelism.

VIRUS

The frequency with which cases of this syndrome are immediately preceded by an influenza-like episode of encephalitis has previously been mentioned. That "influenza" and certain forms of encephalitis are due to virus infection is now common medical knowledge.

116. Rasmussen, A. T.: Effects of Hypophysectomy and Hypophyseal Stalk Resection on the Hypothalamic Nuclei of Animals and Man, A. Research Nerv. & Ment. Dis., Proc. (1939) **20**:245, 1940.

Workers in the field of virus disease [117] contend that certain neurotropic viruses may pass along the nerve pathways connected with the hypothalamus and that they tend to localize in the latter region and there to produce local necrosis, just as in the exanthems focal multiplication of virus occurs in the skin. The occasional association of certain of the manifestations of this syndrome with herpetic disease, previously indicated, suggests a virus origin. Baldino [77] reported a case of vitiligo of the skin of the eyelid and of the iris following herpes of the iris. Davies,[12] in his stimulating résumé of the syndrome, asserted that the herpes virus is a dermoneurotrope and that it may give rise to this form of vitiligo by causing an intraocular inflammation, similar to sympathetic ophthalmia. Bung, in comment on these cases, suggested that the herpes virus is the etiologic agent. As early as 1890, Bock [18a] ascribed inflammatory lesions of ocular structures following influenza to the "virus of influenza." The same author, in an excellent review of the syndrome, called attention to the hypothesis that recurrent iritis with hypopyon associated with an aphthous infection of the genital organs and buccal patches may be due to a virus. There may be some relevance in the case of Noyes, cited by Mauthner,[1b] in which herpes zoster ophthalmicus was followed by destructive uveitis in the left eye and, ten months later, by a similar severe inflammatory process in the previously intact right eye. Jeffries [1b] noted temporary sympathetic disturbance in the fellow of an eye affected with herpes zoster. The striking resemblance of this syndrome to Harada's disease has been commented on by Magitot and Dubois-Poulsen [21e] and by Takahashi.[118] The outstanding features of Harada's disease are the prodrome of general malaise, followed by bilateral uveitis, often with relatively slight involvement of the anterior segment, by diffuse neuroretinitis and, then, by extensive bilateral detachment of the retina; in view of the pronounced intraocular changes, vision after recovery may be surprisingly good. Bilateral detachment of the retina does not occur, however, in the syndrome under discussion, as reported by Laje Weskamp,[19] Arisawa,[119] and Koyanagi.[8] Magitot and Dubois-Poulsen [21e] reported a case showing most of the symptoms of each syndrome. The spinal fluid exhibited marked pleocytosis, comparable to that in my case and in 4 of Takahashi's [118] 6 cases. Magitot and Dubois-Poulsen [21e] concluded that the causative agent in their case was probably a neurotropic virus. They admitted that an epidemic has never been observed, but Schiff-Wertheimer,[120] in discussing the point, mentioned several cases, not completely typical, occurring in a small French village. Laje Weskamp [19] critically appraised the theory that the causative agent is a neurotropic virus and predicted that this hypothesis would find more supporters.

In several respects the similarity of this condition to sympathetic ophthalmia deserves notice. Hutchinson,[6] in a report of historical interest, described an incomplete case of this syndrome as one of "non-traumatic sympathetic ophthalmia." Laje Weskamp [19] and Soriano [21f] pointed out that one manifestation of the syndrome, dysacousia, is sporadically encountered in sympathetic ophthalmia. When it occurred in the latter condition, Komoto [31a] referred to it as sympathetic deafness. Laje Weskamp [19] stated that Peter, who wrote extensively on sympathetic ophthalmia, had expressed agreement with this view. Laje Weskamp [19] stated the belief that poliosis occurs occasionally with sympathetic ophthalmia, and Nettleship [64c] reported the occurrence of poliosis in the course of traumatic sympathetic ophthalmia. Takahashi [118] was struck by the resemblance of this condition both to Harada's disease and to sympathetic ophthalmia. The histologic resemblance of this condition to sympathetic ophthalmia was especially apparent in 1 of 3 eyes microscopically examined.[121] Ogawa,[122] who was cited by Knapp in an abstract of his article, pointed out that the microscopic picture presented by sympathetic ophthalmia is sometimes atypical. The work tending to support the view that this condition is caused by a virus has been partially summarized by Duke-Elder [1a] and includes the positive results obtained in animals with herpes virus by Gifford and Lucic.[123] Although the histologic changes in their animals less closely resembled those of sympathetic ophthalmia than did the clinical picture, the microscopic discrepancy may

117. Sabin, A. B., and Olitsky, P. K.: Influence of Host Factors on Neurosinvasiveness of Vesicular Stomatitis Virus, J. Exper. Med. **66**:15, 1937; **67**:210, 1938.

118. Takahashi, M.: Klinische und experimentelle Studien über das Wesen von sog. idiopathischer doppelseitiger schwerer Uveitis, Acta Soc. ophth. jap. **34**:506, 1930.

119. Arisawa cited by Koyanagi.[8]

120. Schiff-Wertheimer, in discussion on Magitot and Dubois-Paulsen,[21e] p. 227.

121. Jacobi,[64b] in a case of sympathetic ophthalmia, was the first to examine microscopically an eye clinically associated with poliosis of the cilia.

122. Ogawa: Pathology of the So-Called Idiopathic Uveitis with Dysacousia and Poliosis, Acta Soc. ophth. jap. **38**:68, 1934; abstracted, Arch. Ophth. **13**:1089 (June) 1935.

123. Gifford, S. R., and Lucic, L. H.: Sympathetic Uveitis Caused by the Virus of Herpes Simplex, J. A. M. A. **88**:465 (Feb. 12) 1927.

well have been due to the variation in cellular response in different species. Further work demonstrating that either sympathetic ophthalmia or this syndrome is caused by a virus might be construed as throwing light on the etiologic agents of both conditions.

Takahashi [118] injected liquid vitreous from several patients with this syndrome into the cisterna of rabbits. In 2 of the 5 animals receiving such injections optic neuritis and uveitis developed. He also injected cerebrospinal fluid from his patients into the vitreous of rabbit eyes and in a few instances produced uveitis. Experimental transmission from rabbit to rabbit gave positive results. Intracerebral injections in rabbits produced no clinical change. He followed his animals for several months, and even after intraocular injections a slight initial inflammatory reaction was transient enough to be separated by a distinct time interval from the severe uveitis which ultimately developed. In connection with work of this sort, it is helpful, however, to remember that experimental transmission of virus disease is difficult to interpret, and Olitsky [124] stated that accidental contamination of material accounted for some of the positive results reported in this field. Frequently, moreover, virus material will not "take" at first, and it may be necessary to give the animal an injection every three or four days, until a "take" is secured.[125]

Malbrán and Muhlmann [25a] injected vitreous from a patient with Harada's disease into the subarachnoid space of rabbits and reproduced the uveitis and optic neuritis. They also injected spinal fluid from their patient into the vitreous of rabbits and produced intraocular inflammation which, twelve to sixteen days later, appeared in the untreated eye. They ascribed their positive results to a neurotropic virus "similar to the causative organism of herpes or sympathetic ophthalmia."

It is clear that confirmation of this experimental work will be of great importance in the elucidation of the cause of this syndrome, and possibly of sympathetic ophthalmia. Partial justification for the presentation of a speculative paper on this subject lies in the hope that it will lead to the utilization of clinical material as it becomes available.

In the case recently reported by Givner,[126] technics for virus study were employed only with aqueous and iris material, and only more than a year after the prodromal stage.

SUMMARY

In the case reported here, as in other cases of the syndrome, transient encephalitis, the presence of which was proved by examination of the cerebrospinal fluid, was preceded by a sense of superficial irritation of the eyes and general malaise, was accompanied by severe cephalalgia, tinnitus, lethargy, optic neuritis and transient unilateral palsy of the sixth nerve and was followed by nerve deafness, severe bilateral uveitis and certain dermatoneuroses. Vitiliginous areas were observed to fluoresce in ultraviolet light. Later, the patient complained of transient paresthesia and of polyuria.

Evidence that alopecia areata, vitiligo and poliosis are neurodermatoses led to the suggestion that, in the same sense, the intraocular reaction, in which disturbance of ocular pigment is notably prominent, is a neurochoroidosis and that a hypothalamic lesion, the result of encephalitis, might affect retinohypothalamicohypophysial vegetative fibers, possibly neurotropic and afferent to hormonal effectors, and so related to control of pigmentary states. Since it is known that the hypothalamus mediates or regulates certain subcortical levels of consciousness, it appears relevant to the hypothesis that in a case in which prodromal encephalitis was not in evidence the condition was known to follow unusually severe emotional trauma. Further confirmation is found in a case of tumor of the third ventricle, pressing on the hypothalamus, in which practically all these manfestations were noted, including dysacousia, which the authors concluded was adventitious in their case.

Interplay between emotion and infection, and between allergy and vasomotor mechanisms, is known to exist, and cases have been observed in which the neurodermatoses previously mentioned occurred alone and followed intense emotional activity.

Certain other hypothalamic functions appear to be involved in this syndrome.

This disease complex shows similarity to sympathetic ophthalmia with respect to symptoms, including possible dysacousia, and to histologic features, and the evidence exists that either or both may be due to virus infection. Although cisternal inoculation of experimental rabbits did not reproduce the disease in this case, it is known that repeated inoculations of virus materials is frequently necessary to obtain a "take." Further work in other laboratories tending to demonstrate a virus origin is justified.

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124. Olitsky, P. K.: Personal communication to the author.

125. Toomey, J. A.: Personal communication to the author.

126. Givner, I.: Bilateral Uveitis, Poliosis and Retinal Detachment with Recovery, Arch. Ophth. **30**: 331 (Sept.) 1943.

Clinical Notes

AUTOINOCULATION OF THE EYELIDS WITH VACCINIA

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Although ocular complications following vaccination are not rare, they are uncommon, and it is thought timely to call attention to the omnipresent possibility of their occurrence.

Their mode of occurrence may be of two types: autoinoculation, in which there is direct transfer of the virus from the site of vaccination to the eyes; and heteroinoculation, in which the virus is transferred from one person to another.

The lids, conjunctiva or cornea may be involved; of these, involvement of the cornea is most serious, since in this type impairment of vision may result. In approximately one third of the reported cases of vaccinia with ocular complications the cornea has been involved.[1]

Appearance of the patient in a case of autoinoculation of the eyelids following vaccination for smallpox.

REPORT OF A CASE

G. B., an 8 year old white boy, was first seen on May 5, 1943. One week before he had been vaccinated on the right arm. Three days after the vaccination the patient noted redness and swelling of the lids of both eyes. The condition of the lids became progressively worse. At the time the reaction of the lids was first noted, an inflamed area developed on the chin, which gradually progressed to a typical vaccinia reaction.

Examination of the lids of both eyes showed pronounced redness, swelling and induration, with several ulcerations along the margins. There was moderate mucopurulent discharge. The conjunctiva of the right eye was mildly injected; that of the left eye was chemotic as well. The cornea did not stain with fluorescein. There was nontender swelling from eye to ear bilaterally.

A tentative diagnosis of vaccinia reaction was made. Subsequent stained smears and cultures of the discharge were negative for any causative organisms, and with the presence of the typical reaction of vaccinia on the arm and chin, the diagnosis was felt to be justified.

The temperature at the time of admission was 101 F. Sulfadiazine was administered orally, and within eight hours the temperature was essentially normal and remained so throughout the stay in the hospital, although administration of the sulfadiazine was discontinued in twelve hours.

Irrigations of boric acid were made every hour during the day, together with application of hot compresses for twenty minutes three times a day. Under this treatment there was decided improvement over the course of five days. At the time of discharge there was no edema of the lids of the right eye, no conjunctival injection and no corneal involvement, although there were three areas of excoriation with crust formation on the lower lid. The left eye showed mild edema of the lower lid and excoriation of the margin of the lid, with crust formation across its entire extent. The patient was discharged, with instructions to use hot compresses three times a day, followed by instillation of aqueous solution of metaphen (1:2,500).

COMMENT

Sulfadiazine was used for a short time in this case, since the diagnosis was at first questionable. Its use was discontinued after examination of smears revealed no causative organisms, and its effect was probably only to reduce the febrile reaction. In this respect, Atkinson and Scullard [1] reported that azosulfamide, sulfanilamide and sulfapyridine do not prevent the usual vaccinia reaction in rabbits.

As stated by Laval,[2] the sooner the secondary inoculation follows the primary one, the more severe and the more prolonged is the secondary reaction. In the case just reported this fact is well illustrated, since the secondary reaction

1. Atkinson, W. S., and Scullard, G.: Vaccinia with Ocular Involvement, Arch. Ophth. **23**:584 (March) 1940.

2. Laval, J.: Vaccinia of the Eyes, Arch. Ophth. **24**:367 (Aug.) 1940.

began only three days after vaccination, and there was a fairly severe constitutional response, as well as a rather marked reaction of the lids and conjunctiva.

It is important that inoculation of the cornea be prevented if possible, and measures should be taken to prevent the patient from rubbing or scratching the eyes.

Lesions of the lids and conjunctiva have been found to run a self-limited course, healing in seven to ten days, with no sequelae. Corneal involvement, however, requires a much longer period for healing, and visual impairment often results.

SUMMARY

In the case of autoinoculation of the eyelids following vaccination for smallpox here reported, the lesions healed without complications within the usual self-limited period.

It is of the utmost importance to prevent corneal involvement.

University Hospital.

Ophthalmologic Reviews

EDITED BY DR. FRANCIS HEED ADLER

OCULAR TUBERCULOSIS

ITS RELATION TO GENERAL TUBERCULOSIS

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There can no longer be any question that tuberculosis has prevailed from earliest times. The Old Testament perhaps refers to it when it alludes in three places to consumptive diseases (*shapahath*).[1] Among the symptoms are mentioned extreme wasting of the body and phthisis bulbi. In "Zechariah" the disease is described as follows: "In this shall be the plague . . . the flesh shall consume away, and the eyes shall consume away in their holes." In order to gain a clear knowledge of the history of tuberculosis of the eye, it is pertinent to present a brief historical sketch of general tuberculosis.

GENERAL REVIEW

As far back as the days of Hippocrates tuberculosis was recognized as a disease characterized by the breaking down and destruction of tissues. The name "phthisis," from the Greek word φθισις, meaning "wasting away," or "decay," was applied to this malady by Hippocrates. The father of medicine considered patients afflicted with this disease as incurable: "Many, and in fact, most of them died; and of those confined to bed I do not know of a single individual who survived for any considerable time."[1a] His description of the so-called facies hippocratica gives a typical picture of the last stage of consumption: "Hollow eyes, sharp nose, sunken temples, tense skin, cold ears, parched and discolored face, livid eyelids, open mouth and blanched lips."[1a]

Hippocrates had no other diagnostic procedures at his disposal than simple inspection and palpation. He had no stethoscope and no experience in percussion and auscultation. He had no tuberculin, no microscope and no roentgen rays to confirm his diagnosis. In spite of all these handicaps, his diagnoses appear to have been correct, and his therapeutics was far in advance of his time. He advised a young patient suffering from consumption to leave the city and rest in the sunshine, to eat nutritious foods and to imbibe much milk until his flesh rounded his frail frame and until his cough was gone and strength had returned. He stated the belief that phthisis was caused by small foci of pus.

Of the later ancient medical writers, none surpasses Aretaeus (about 50 A. D.) in his vivid description of tuberculosis. In his book *"De causis et signis morborum"* (The Causes and Diagnosis of Disease), he described with extraordinary accuracy:[2]

> . . . the curved nails, shrunken fingers, slender, sharpened nostrils, hollow, glazy eyes, cadaverous look and hue, the waste of muscles and startling prominence of bones, the scapulae standing off like the wings of a bird; the thin, veneer-like frames, the limbs, like pinions, the prominent throats and shallow chests.

He remarked that "moist and cold climates are the haunts of it."

Incidentally, Aretaeus was the first to make the following striking observation:[2]

> . . . Hemorrhage from the lungs is particularly dangerous, although patients do not despair even when near their end. The insensibility of the lungs to pain appears to me to be the cause of this, for pain is more dreadful than precarious; whereas in the absence of it, even serious illness is unaccompanied by fear of death and is more dangerous than dreadful.

The external signs of habitus phthisicus, which were described in great detail by ancient medical writers, have not changed up to the present time. Indeed, that frail, undersized, emaciated body, with the long, narrow, flat chest, in which the ribs stand out prominently, the chest bone is depressed and the shoulder blades project in the back like two wings, is the classic description

Read at a meeting of the Medical Staff of the Atlantic County Hospital for Tuberculous Diseases, Northfield, N. J., May 18, 1942.

1. Leviticus 26:16. Deuteronomy 28:22. Zechariah 14:12.

1a. Robinson, V.: The Story of Mankind, ed. 5, New York, Tudor Publishing Company, 1936, p. 510.

2. Aretaeus, cited by McLintock, J., and Strong, J.: Biblical Theological and Ecclesiastical Cyclopedia, New York, Harper and Brothers, 1894, vol. 6, p. 32.

still applicable to a large number of patients with tuberculosis.

There is no evidence that Hippocrates suspected contagion or infection to be the cause of these symptoms, although his contemporary, the historian Thucydides, in his "History of the Peloponnesian War," expressed a definite belief in the infectious character of plague and its transmission from one person to another. Describing the plague of Athens, he stated: "Nay, they [physicians] themselves died most of all, inasmuch as they most visited the sick."

Galen [3] indicated the infectious character of consumption when he stated that it is a matter of experience that persons who sleep in the same bed with tuberculous patients, as well as those who live long with them or wear their clothes and use their linens, contract tuberculosis.

In the hippocratic works, coxitis (tuberculous hip joint disease) is referred to, and its symptoms are correctly described: local and reflex pain coming on spontaneously, especially on movement of the limb; stiffness of the hip joint and the vertebral bones; lordosis (anterior convexity of the spine); bone necrosis; abscess formation, and spontaneous dislocation of the joint. The prognosis of coxitis, according to hippocratic writers, is poor as far as the use of the limbs is concerned. When ankylosis takes place, the limb becomes paralyzed. The hippocratic treatment consists of regulation of diet, internal administration of iron preparations and bleeding.[4]

Tuberculous bone disease was the scourge of the ages, even before pulmonary tuberculosis was recognized. Spondylitis, or tuberculosis of the spine, first described by Pott [5] (1713-1788) prevailed among ancients five millenniums ago.

While excavating in Grenelle, France, Palès [6] found two neolithic skeletons, one showing evidence of tuberculosis of the hip and the other signs of tuberculosis of the spine. Hofschlager [7] cited Bartel's statement to the effect that a neolithic skeleton from Heidelberg exhibited Pott's disease with kyphosis. Smith and Ruffer [8] recorded a case of Pott's disease in an Egyptian priest of Ammon of the twenty-first dynasty (about 1000 B. C.). In 1 case, Ruffer,[9] in a histologic study, noted an abscess of the right psoas muscle. Derry, according to Smith and Jones,[10] reported the discovery of several tuberculous spines at Thebes, dating from the twenty-third dynasty. Palès [6] mentioned the case of a child with coxalgia from the fifth dynasty and the case of an infant with a tuberculous hip, of 1900 B. C.

In America, Moodie [11] found Pott's disease in a Peruvian skeleton dating from prehistoric times. He expressed the opinion that the Peruvian Indians were widely afflicted with tuberculosis.

While Pott's disease is at present known to be caused by tuberculous infection of the spinal vertebrae, Percivall Pott, who first described the pathologic condition, attributed it to "scrofulous diathesis," which attacks children between the ages of 3 and 10 years. Many pathologic conditions known at present to be caused by the tubercle bacillus were attributed to various causes and were designated as different diseases. Thus, the term "scrofula" was applied to a number of pathologic conditions affecting the lymph glands of the neck, to various inflammatory diseases of the eyes and to chronic infections of the nose and throat. Tuberculosis of the lungs was designated by the name "consumption," "phthisis" or "white plague." Tuberculosis of the intestinal canal was known as "tabes mesenterica"; tuberculosis of the skin and eyelids, as "lupus"; tuberculosis of the conjunctiva, as "phlyctenules," or "phlyctenular conjunctivitis"; tuberculosis of the cornea, as "phlyctenular keratitis"; tuberculosis of the spine, as "Pott's disease," and tuberculosis of the bones and lymph glands, as "struma," "scrofula" or "king's evil."

While persons with phthisis were readily recognized as early as the days of Hippocrates, the world had to wait until the close of the seventeenth century for Franciscus de le boe Sylvius (1614-1672) to recognize the "little lumps" present in the tissue of consumptive

3. Galen believed in aerotherapy for tuberculosis. He ordered his patients to warm climates and to the sunny slopes of Vesuvius.

4. Lurje, S.: Studien über Chirurgie der Hippokratiker, Dorpat, C. Mattiesen, 1890, p. 117.

5. Pott recognized the cause of the disease, at least to the extent of calling it scrofula. His first paper on the subject bears the long title "Remarks on That Kind of Palsy of the Lower Limbs, Which Is Frequently Found to Accompany a Curvature of the Spine" (London, J. Johnson, 1779).

6. Palès, L.: Palèopathologie et pathologie comparative, Paris, Masson & Cie, 1930.

7. Hofschlager, R.: Von den Krankheiten des Vorgeschichtlichen Menschen, cited by Krogman, W. M.: The Pathology of Pre-and Proto-Historic Man, Ciba Symposia, May 1940.

8. Smith, G. E., and Ruffer, M. A.: Pott'sche Krankheit an einer ägyptischen Mumie aus der Zeit der 21 Dynastie (um 1000 v. Chr.), in Sudhoff, K. F., and Sticker, G.: Zur historischen Biologie der Krankheitserreger, Giessen, A. Töpelmann, 1910, no. 3, pp. 9-16.

9. Ruffer, M. A.: Studies in Paleopathology of Egypt, edited by R. L. Moodie, Chicago, University of Chicago Press, 1921.

10. Smith, G. E., and Jones, F. W.: The Archeological Survey of Nubia: Report for 1907-1908, Cairo, National Printing Department, 1910, vol. 2.

11. Moodie, R. L.: Paleopathology, Urbana, Ill., University of Illinois Press, 1923.

patients and to present an accurate description of their pathologic character. In the performance of a number of autopsies, Sylvius was impressed by the frequent occurrence of small, rounded, whitish gray bodies in the lungs of patients who in life had a condition diagnosed as phthisis. Sylvius came to the decision that these round bodies were the cause of phthisis. His conclusion was particularly prompted by the fact that pus commonly accompanies phthisical sputum; he compared these nodules with the commonly observed pus-producing inflammatory elevations, or papules, on the surface of the body. His explanation as to how and why they arose in the lungs and how they caused phthisis, however, is not conclusive, for his etiologic factors did not include the tubercle bacillus.

In the middle of the seventeenth century, the problem of tuberculosis attracted the serious attention of such celebrities as Thomas Sydenham (1624-1689), Thomas Willis (1621-1675) and Richard Morton, of England. Morton, in 1689, stated the opinion that the small bodies noted in the tissue started the ulcerative process in the lung. He also stated that one could die of the disease without showing any evidence of the small bodies, as they might be invisible. This last assertion anticipated the German maxim of later years, "Jedermann hat ein bischen Tuberculose am Ende." Other famous physicians interested in the subject were Gerard van Swieten, Boerhaave and Paul Barbette, of Netherlands; Jacob Manget, of Geneva, Switzerland; Sauvages, of France, and the famous anatomist, Giovanni Battista Morgagni, of Italy. The last investigator, while doing many autopsies in his anatomic studies, admitted that he had performed few on persons who had died of phthisis, adding that his master, Valsalva, had done practically none. It was not shortage of material that prevented autopsies on tuberculous cadavers. Morgagni readily admitted his great fear of contracting the disease from cadavers. He advised his young students also to shun them.

The association of these "little lumps" with consumption was proved by William Stark, a pupil of John Hunter, who, in 1785, while describing what is now known as miliary tuberculosis, pointed to these lesions as the cause of the disease, thus anticipating much that Laënnec was later to discover concerning tuberculosis. But Stark's work fell on deaf ears. The connection of these "little lumps" with consumption became a subject of controversy among students of pathology of various countries, among whom may be mentioned Cullen and Baillie, of England, and Portal, Kortum, Corvisart and Bichat, of France.

Bichat (1771-1802) died of tuberculosis, at the age of 31 years. One of his last utterances was: "Not much is really known about the pathology of phthisis, for few autopsies have been done because of the foolish fear among physicians that the disease is catching." His early death proved that phthisis was contagious. This brilliant scientist has been called the Napoleon of medicine. When his teacher, Corvisart (1755-1821), wrote to Napoleon: "Bichat has just fallen on a battlefield which numbers more than one victim; no one had done so much and so well in so short a time," the Corsican ordered the bust of Bichat placed in the Hotel Dieu.

The first to call attention to phthisis of the eye was Antoine Maître-Jan [12] (born 1650), a

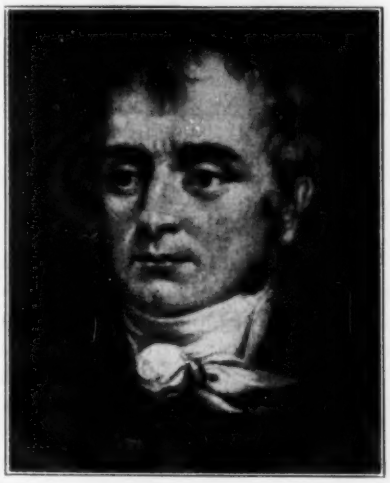

Fig. 1.—Marie François Xavier Bichat (1771-1802). From an engraving by H. Cook in Pettigrew's Medical Portrait Gallery, in the collection of the New York Academy of Medicine.

celebrated French physician of the seventeenth century. In 1707 he described the case of a soldier in whose eye an excrescence of the iris had sloughed through the cornea, and he attributed the condition to phthisis of the eye. He did not make clear on what grounds he based his conclusion. A century passed before the relation of ocular disease to phthisis of other organs of the body was pointed out again, this time by Autenrieth,[13] who described a choroidal tumor in a man who died later of generalized tuberculosis.

12. Antoine Maitre-Jan, sometimes known as the father of French medicine, author of "Traité des maladies de l'oeil, et des remèdes propres pour leur guérison," Troyes, J. le Febure, 1707 (p. 456); ed. 2, Paris, L. d'Houry, 1722; Paris, Breton, 1740.

13. Autenrieth, J. F. H.: Versuche für die praktische Heilkunde, Tübingen, J. G. Cotta, 1807, vol. 1, p. 309.

About the same time Gaspard Laurent Bayle (1774-1816), in his "Recherches sur la phthisis pulmonaire" (1810), described the "millet seed" bodies which he observed in cases of phthisis, calling them "tubercles," and he ascribed the pathologic changes in the patient to the process of caseation and to softening of the tubercles

Fig. 2.—René Théophil Laënnec (1781-1826). From an unsigned lithograph in the collection of the New York Academy of Medicine.

which he saw in many organs. After long and arduous clinical studies and hundreds of post-mortem examinations of persons who had died of tuberculosis, he came to the conclusion that phthisis is an infectious disease and that the infection is caused by the inhalation or swallowing of poisonous material given off by persons suffering from this disease. Bayle himself died of tuberculosis in 1816, at the age of 42.

His intimate friend and junior collaborator, René Théophile Laënnec (1781-1826), continued the investigation where Bayle left off. In spite of violent opposition from high places in the medical world, he supported Bayle's views and corroborated them with new evidence. He, too, made hundreds of autopsies, in many of which he observed diseased areas containing the "little lumps." Both investigators established the relation of these tubercles in the lungs to pulmonary phthisis and gave to them the name of tubercles. Bayle and Laënnec were convinced that these tubercles can be seen not only in the lungs but in any part of the body: skin, intestine, bones, brain, eyes and mucous membranes.

Laënnec demonstrated that phthisis not only hampers the organ it affects but produces a poison which spreads and affects the whole body, thus producing the symptoms characteristic of the disease. With the use of a microscope, but without the knowledge of the cell as the unit of tissue (the cell doctrine was promulgated in 1836), Laënnec maintained that the several forms of the disease depend on the development of the millet seed bodies. His ideas were accepted almost everywhere. He graphically described the tubercle as a "body composed of a gray, gelatinous form of infiltration, sometimes involving a whole lobe of a lung." The basis of all modern knowledge of tuberculosis, save only the important fact that the tubercles are produced by the action of the tubercle bacillus, came from Laënnec's researches.

About the same time, the famous Italian anatomist and ophthalmologist Scarpa[14] described the case of a patient with an ocular condition which did not respond to local treatment as that of scrofulous ophthalmia of systemic origin. That the term "scrofulous ophthalmia" was applied to ocular phthisis may be inferred from the statement of the English ophthalmologist Mackenzie,[15] who, in 1830, while describing a case of conjunctivitis (which was probably phlyctenular conjunctivitis), asserted that "other scrofulous symptoms may be detected in almost every stage of the disorder, including disease of the joints, and tabes mesenterica."[16] The term tuberculosis was first used in 1839, by Dr. J. L. Schoenlein, of Zurich, Switzerland.

In 1831 von Jaeger[17] reported a case of tuberculosis of the eye in which the disease spread from the ciliary body, perforated the globe and produced phthisis bulbi. The diagnosis of

Fig. 3.—Antonio Scarpa (1752-1832).

14. Scarpa, A.: Treatise on the Principal Diseases of the Eyes, translated by J. Briggs, London, T. Cadell & W. Davies, 1818.

15. Mackenzie, W.: A Practical Treatise on Diseases of the Eye, London, Longman [and others], 1830, p. 387.

16. Tabes mesenterica has always been considered of tuberculous origin.

17. von Jaeger, cited (page 2318) by W. S. Duke-Elder, from whose monumental work "Text-Book of Ophthalmology" (St. Louis, C. V. Mosby Company, 1941, vol. 3) I have derived valuable information in preparing this paper.

tuberculosis was confirmed after the enucleation of the organ of vision.

Prior to the middle of the nineteenth century the nature of ocular disease could only be surmised from the external appearance of the eye. Such gross changes as inflammation of the ocular tissues, discoloration of the cornea and impaired vision all too frequently occur only when disease

Fig. 4.—William Mackenzie.

is far advanced. The diagnosis of internal disease of the eye was largely speculative, the true character of the malady becoming obvious only after enucleation or during postmortem examination of the body. The difficulty in arriving at a correct diagnosis of ocular disease came from the lack of any adequate mechanical devices with which to determine pathologic changes in a living eye and to identify the location of such changes before the disease was well advanced.

The invention of the ophthalmoscope in 1851, by Hermann Ludwig Ferdinand von Helmholtz (1821-1894), an instrument which disclosed the deep structures of the eye and made clear any deviations from the normal state, not only revolutionized the field of ophthalmology but opened a new portal to the clinician in general. Many diseases of systemic origin and doubtful character became accurately diagnosed entities with the invention of the ophthalmoscope.

It may not be out of place here to quote von Helmholtz' own story of how he came on the idea of the ophthalmoscope: [18]

> While preparing for the lecture, I first hit on the possibility of the ophthalmoscope . . . the ophthalmoscope has become the most popular, perhaps, of my scientific achievements, but I have already told the ophthalmologists how luck played an incomparably greater part than merit in this matter. I had to explain to my students the theory of ocular luminosity, which stemmed from Brücke. Actually, Brücke had missed the discovery of the ophthalmoscope by a hair's breadth. He had only neglected to ask himself the question: To which optical image do the rays returning from the luminous eye belong? Had he raised this question, he could have answered it just as quickly as I did, and the ophthalmoscope would have been discovered. I was considering the problem from different angles, in order to see how I could present it most simply to my audience, and while so engaged I hit upon the aforementioned question. As a result of my medical studies, I was well acquainted with the difficulties confronting ophthalmologists in those conditions which at that time were lumped together under the term amaurosis. I immediately set about to construct the instrument out of spectacle lenses and cover glasses for microscopic preparations. At first it was still quite difficult to use, and without a firm theoretic conviction that it must work, I would perhaps not have persevered in my efforts. But after about eight days I had the great pleasure of being the first to see clearly a living human retina.

As has often been the case with medical innovations, his discovery did not receive undivided support from members of the medical profession. One distinguished ophthalmologic colleague told the discoverer that he should never use the instrument, for it would be too dangerous to admit naked light into the diseased eye! Another expressed the opinion that the mirror

Fig. 5.—Fred von Jaeger (1784-1871).

might be of service to oculists with defective eyesight. For his part, he had good eyes and wanted none of it.

After the discovery of his Augenspiegel, not a year passed that von Helmholtz did not make some new discoveries. His investigations delved into the realms of physics, physiology, medicine, optics, chemistry, acoustics, electricity and

18. Von Helmholtz was preparing a lecture for his class at the University of Königsberg, where he occupied the chair of physiology, on the subject of ocular luminosity in certain animals, such as the rabbit and cat (Erinnerungen, in Vorträge und Reden, Braunschweig, F. Vieweg & Sohn, 1896, vol. 1). His modesty, refined life and simple taste he inherited from his mother, who was a Hanovarian lady, a lineal descendant of the great Quaker, William Penn.

mathematics. His work "Physiologic Optics" (1856-1860) is by far the most important book that has ever appeared on the physiology and physics of vision. By his invention of the ophthalmometer, he measured the radiuses of curvature of the crystalline lens for near and far vision. He investigated the mechanism of accommodation by which the eye can focus within certain limits and the movements of the eyeballs necessary to secure single vision with two eyes. He revived and gave new force to the theory of color vision associated with the name of Thomas Young, based on the three primary colors, and he applied the theory to the explanation of color blindness. The most important of his discoveries, however, was the ophthalmoscope. When von Graefe first saw the fundus of the living eye, he exclaimed, "Helmholtz has unfolded to us a new world."

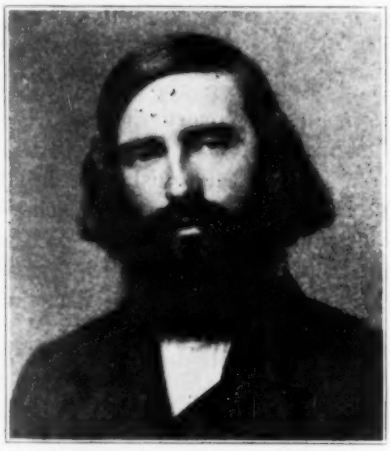

Fig. 6.—Albrecht von Graefe (1828-1870).

Four years after the invention of the ophthalmoscope, Albrecht von Graefe (1828-1870) and Friedrich Moritz H. Heymann (1828-1871) described renal retinitis, thus corroborating the diagnosis of the internist, or even calling his attention to the fact that the patient's ophthalmic condition was due to renal dysfunction. In 1853, two years after the invention of the ophthalmoscope, Coccius observed detachment of the retina, and in 1855 Liebreich noted thrombosis of the central vein. In 1860 von Graefe observed bilateral papilledema and embolism of the central artery. A new conception of glaucoma was made possible, and the cause of amaurosis in cases in which the external portion of the eye exhibited no pathologic signs—a problem throughout the ages—at last became known.[19]

19. Sorsby, A.: A Short History of Ophthalmology, London, John Bale, Sons & Danielsson, 1933, p. 81.

What the discovery of roentgen rays, fifty years later, has been to pulmonary tuberculosis, the invention of the ophthalmoscope was to ocular tuberculosis. Five years after von Helmholtz' invention, Jaeger observed tubercles in the choroid with the ophthalmoscope.[17] The tuberculous character of these lesions was corroborated microscopically by Manz[20] (1858), who first reported the case and recorded 2 additional ones in 1866. Cohnheim[21] (1867) demonstrated that the choroidal nodules seen in the eye clinically were pathologically identical with the tubercles seen elsewhere in the body. His investigations proved that they occur more frequently than had been supposed. Similar conclusions were reached by von Graefe and Leber, in Germany (1868), and by Wells, in England (1868).[22] In 1874 Köster[23] described tubercles of the conjunctiva. About the same time Horner[24] diagnosed with the ophthalmoscope for the first time conglobate tubercles of the choroid in man. Some time later Jessop[25] described a case of tuberculous conjunctivitis following injury.

The recognition of tuberculosis was greatly advanced by the investigations of Jean Antoine Villemin (1827-1892).[26] Villemin demonstrated the infectious nature of the tubercle by injecting tuberculous tissue into rabbits. He told his assistants in the army in which he was a surgeon that "the phthisical soldier is to his messmate what the glanderous horse is to his yoke fellow." Villemin was first to observe that the tubercles were caused by living entities. He was, however, unable to identify the etiologic factor with his microscope.

Soon after, von Baumgarten[27] inoculated the anterior chamber of rabbits with tuberculous tissue and, after removing the eyes for histologic study, observed that migratory cells gather

20. Manz, W.: Tuberculose der Chorioidea, Arch. f. Ophth. **4** (pt. 2):120, 1858.

21. Cohnheim, J.: Ueber Tuberculose der Chorioidea, Arch. f. path. Anat. **34**:49, 1867.

22. von Graefe, A., and Leber, T.: Ueber Aderhauttuberkeln, Arch. f. Ophth. **14** (pt. 1):183, 1868.

23. Köster, cited by Harman,[31] p. 140.

24. Horner, cited by Haab, O.: Atlas and Epitome of Ophthalmoscopy and Ophthalmoscopic Diagnosis, edited by G. de Schweinitz, Philadelphia, W. B. Saunders Company, 1909, page opposite figure 76.

25. Jessop, W. H.: Tuberculosis of the Conjunctiva, Tr. Ophth. Soc. U. Kingdom **20**:51, 1900; in Carpenter, G., and Stephenson, S.: Tuberculosis of the Choroid, in Reports of the Society for the Study of Diseases of Children, London, J. & A. Churchill, 1900-1901, vol. 1, p. 169.

26. Villemin, cited by Piersol, G. M., and Bortz, E. L.: Cyclopedia of Medicine, Philadelphia, F. A. Davis Company, 1935, vol. 12, pp. 232-244.

27. von Baumgarten, P., cited by Flick, L. F.: Tuberculosis, Philadelphia, The Author, 1937, p. 69.

around the infected material, with tubercle bacilli crowded in the center.

Knowledge of the etiologic agent of tuberculosis, which Sylvius, Laënnec and Villemin attributed to the tubercles observed in the diseased tissues, reached its climax with the great discovery of Robert Koch (1843-1910), who in

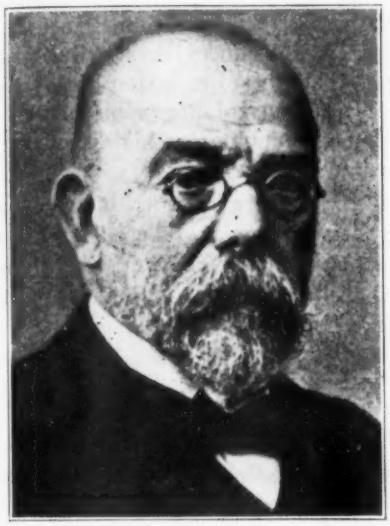

Fig. 7.—Robert Koch (1843-1910). From a photoengraving in the collection of the New York Academy of Medicine.

1882 stirred the scientific world by the announcement of his discovery of a living organism (the tubercle bacillus) in sections of the tubercles. He proved the accuracy of his observations by producing tuberculosis in guinea pigs inoculated with cultures of this bacillus. Koch, however, had a difficult task to convince his medical colleagues that he had made a momentous discovery, for he was unknown to the scientific world. He suddenly emerged from obscurity, to be ranked among the greatest scientists of his age.

A short biographic sketch of Koch may be apropos at this point. There was nothing eventful in his early life. His family was in modest circumstances. There was little reserve for luxuries or for giving the children a higher education. When young Robert was about to finish the local high school, his parents planned for him to learn the shoemaking trade. Just then an unforeseen improvement took place in the financial condition of the elder Koch, which enabled him to send his son to the University of Göttingen, where the celebrated pathologist (Frederick Gustave) Jacob Henle (1809-1885), the author of "A Handbook on Rational Pathology," was professor. At that period Henle published his famous essay, entitled "Miasmata and Contagia," which was widely discussed in scientific medical circles. It contained the first clear statement in modern terms that infectious diseases are due to specific organisms. It is likely that this famous teacher had a great influence over young Koch's future work.

After receiving his doctorate, Koch disappeared from academic circles for ten years. His meager financial status compelled him to earn a livelihood immediately. He started his medical career as an obscure country doctor in the little town of Wollstein, in the province of Pausen, Czechoslovakia. This town had a mixed population, made up largely of Czechs and Poles. There were certainly no laboratory facilities. All that he possessed was a microscope, which he had purchased while at the university. One can be certain that he used it at his office whenever he could spare time from his medical duties.

In those days bacteriology was a branch of botany, and the leading authority on that subject was Ferdinand Cohn, of Breslau. Any one who wanted information on the parasitism of the algae and fungi applied to Ferdinand Cohn. From a letter sent to Cohn by Koch in 1876, it is clear that the latter did not spend his ten years in Wollstein idly. The letter reads: "After many vain attempts, I have finally been successful in discovering the process of development of the anthrax bacillus. After many experiments, I believe that I am able to state the results of these researches with sufficient certainty. Before, however, I bring this into the open, I respectfully appeal to you, esteemed Herr Professor, as the foremost authority on bacteria, to give me your judgment regarding this discovery."

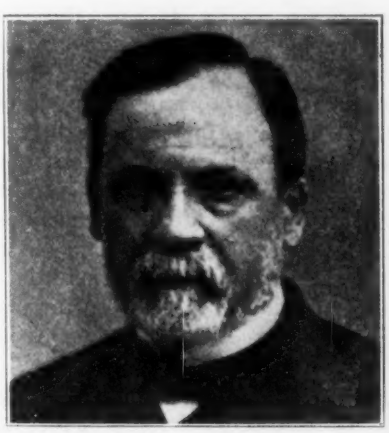

Fig. 8.—Louis Pasteur (1822-1895). From a photograph in the collection of the New York Academy of Medicine.

The epoch-making discoveries of Pasteur undoubtedly had a great influence on Koch's re-

search. One evening, he read in a scientific journal that this French chemist had demonstrated that microscopic plant germs could live and thrive in the bodies of men and animals and that the presence and growth of some of them were attended by disease. Soon afterward, Koch seriously began the task of developing new technical methods, which became the basis of modern bacteriologic technic. He separated and identified bacteria; he grew them in pure culture; he stained them and photographed them.

Koch and his colleagues demonstrated that the tubercles described seventy-eight years before by Laënnec, and fifteen years before by Villemin, were caused by the action of bacteria on the tissues, and that the dissemination of the disease was produced by the spread of these tubercle-forming bacilli.[28]

It was on the evening of March 24, 1882 that Koch startled the Physiological Society of Berlin by announcing his discovery of the tubercle bacillus. He was not satisfied with merely discovering the cause of tuberculosis. He tried to find means of preventing and curing this disease. In 1890 he prematurely announced that he had discovered a remedy for tuberculosis, which revelation was received with great enthusiasm everywhere. As a therapeutist, however, he failed to fulfil the expectation and hope which his announcement raised among millions of people. Although his tuberculin as a therapy for tuberculosis was a failure, the discovery proved to be of diagnostic value. It furnishes a test for the detection of the presence of either active or arrested tuberculosis in the body, although it does not differentiate between the two grades of the disease and does not show the place where the pathologic condition is located. Five years after Koch's discovery (1887), Becker,[29] of Heidelberg, observed a growth in the choroid, just behind the ciliary region, of typical tuberculous structure containing bacilli. He noted smaller tubercles in other parts of the choroid.

The last link in the chain surrounding the diagnosis of tuberculosis came with the discovery of roentgen rays, in 1895, by Wilhelm Conrad Roentgen, professor of physics at the University of Strasbourg, who, while experimenting with electric discharges passing through vacuum tubes, discovered this peculiar kind of energy. This disclosure came to him unexpectedly. One day, while examining a vacuum tube in a black box, he noticed that a paper screen, covered with barium platinocyanide, which accidentally stood nearby, became fluorescent. His curiosity became aroused at this strange spectacle. He soon discovered that the unknown radiations from the tube could pass through substances ordinarily opaque to light and that these radiations possessed the power of affecting photographic plates. Two months later he announced his discovery, which he named x-rays.

Roentgen rays are of only indirect value in the diagnosis of ocular tuberculosis, however; their importance lies in their identifying and localizing tuberculous conditions in other tissues of the body.

RELATION OF OCULAR TUBERCULOSIS TO TUBERCULOSIS IN OTHER ORGANS OF THE BODY

While, as has been shown, the eye, like other organs of the body, may be attacked by the tubercle bacillus, the method of attack has not yet been definitely established. That ocular tissue reacts to micro-organisms and toxins originating from a remote part of the body cannot be disputed. Cases of metastatic ophthalmitis are known to have resulted from pyogenic bacteria carried to the eye by the blood and lymph centers from infected areas of near and distant organs. Iridocyclitis has often been traced to gonorrheal prostatitis, and the gonorrheal chacacter of the infection was demonstrated by many observers. Deutschmann demonstrated gonococci in the mucous discharge of the conjunctiva, which he thought entered the eye by metastasis. A similar observation was made by Parinaud and Duane.[29a] Morax stated that scattered gonococci may be seen in cases of gonococcic conjunctivitis, and that one must not conclude from a negative examination for gonococci that the inflammation is due to pure toxin. The organisms themselves, although not found, cannot be excluded. McKee[29b] reported a case of metastatic gonorrheal conjunctivitis in which the gonococcus was demonstrated.

I have recently observed a similar case in a young man, in Atlantic City, N. J. On the other

28. Koch laid down three cardinal rules with reference to bacteria: 1. A specific organism must be present in all cases of the disease. 2. It must be cultivated in pure culture. 3. It must produce the same disease when injected in healthy animals.

29. Becker, cited by Neese, E.: A Contribution to Tuberculosis of the Eye, Arch. Ophth. **16**:434, 1887.

29a. Fuchs, E.: Textbook of Ophthalmology, authorized translation from the eleventh and greatly enlarged edition of the German by Alexander Duane, ed. 3, Philadelphia, J. B. Lippincott Company, 1908.

29b. McKee, S. H.: Demonstration of the Gonococcus in Smear and Culture, Ophthalmology **7**:462 (July) 1909.

hand, Arnold Knapp, in a number of cases under his observation, could not find gonococci in the conjunctiva, and cultures were sterile. Spirochetes have been observed in the eyes of persons affected with syphilis in other parts of the body; but the tuberculous origin of many obscure ocular diseases attributed to the tubercle bacillus has never been adequately demonstrated.

Those who have the opportunity of observing tuberculous patients in institutions have been surprised at the infrequency of ocular disease among inmates. The eye appears to possess a peculiar immunity to tuberculous infection among patients with pulmonary and other forms of tuberculosis. Both the intrinsic spread of the bacilli and the extrinsic dissemination via the sputum appear to have a negligible effect on the visual organs. Treponema pallidum in its active state readily attacks the uvea and the optic nerve irrespective of the location of the initial lesion, and the gonococcus of Neisser, which usually lodges in the genital organs, frequently involves the conjunctiva; but the bacillus of tuberculosis in the lungs or other tissues of the body seldom affects the eye. In the institutions for the blind may be seen many children who were blinded in consequence of acquired or inherited syphilitic infection or as a result of ophthalmia neonatorum. But cases of blindness due to the tubercle bacillus are rarely seen in such institutions.

Von Michel was the first in Germany to demonstrate the presence of tubercle bacilli in the eye. Since his time many workers, by injecting living or dead tubercle bacilli into the carotid artery of rabbits, have succeeded in producing acute and chronic forms of iritis, tubercles in the iris, nodules on the pupillary margins and circumscribed infiltrates in the cornea. The condition produced by this method showed a striking resemblance to certain chronic forms of clinical iritis, an observation in support of the conclusion that the latter is often tuberculous. (Von Michel, however, did not accept the importance of tuberculin therapy, as suggested by von Hippel.)

Denig,[30] who was an assistant to von Michel in 1895, observing this strange phenomenon of the tubercle bacilli on the human eye, was prompted to declare that tuberculosis of the eye is seldom observed among persons with active tuberculosis of the lungs. In an analysis of 65 cases of pulmonary tuberculosis, 90 cases of tuberculosis in the joints and bones and 20 cases of tuberculosis of the lymph glands, a total of 175 cases of active tuberculosis, Denig found only 5 cases of ocular metastasis, while of 86 cases in which the anterior uveal tract was affected, no evidence of systemic disease was apparent in 76.

In England, Harman[31] (1908) asserted:

> The infection of the eye and of its accessory structures by the tubercle bacillus is one of the rarer forms of disease of which the eye is liable. If we compare the frequency of the effects of this infection with that of another organism—the spirochaeta pallida—which also produces granulomatous inflammations, there can be no hesitation in asserting that tuberculous diseases of the eye are rare.

Whitehead, another English ophthalmologist, in postmortem examinations of patients with ocular tuberculosis who subsequently died of fatal injuries in World War I, noted that 42 per cent exhibited no pathologic lesion elsewhere in the body. The same report came from Egypt. Wilson[32] stated that within seventeen years 21 cases of ocular tuberculosis were recorded by the pathologists of the Government Ophthalmic Hospital. In none of these cases did the surgeons notice any signs of tuberculosis in other parts of the body.

In an analysis of 72 cases of uveal disease in adults, Rohrschneider and Reiners[33] observed minor, dormant and closed remnants of tuberculous processes in 64 cases. In 6 other cases formerly active pulmonary tuberculous foci were inactive at the time of examination. In only 2 cases was active tuberculosis present. These authors found no difference betweeen the cases associated with positive clinical signs of pulmonary tuberculosis and those with less suspicious evidence. They consequently asserted that a diagnosis based on the presence of tuberculous foci in cases of ocular disease is not conclusive. They cited Marchesani,[34] who expressed the opinion that the tuberculous origin of chronic uveitis is not as well established as has been assumed by many authors. Marchesani particularly questioned the tuberculous origin of recurring vitreous hemorrhages in adolescence and suggested that the possibility of Buerger's disease should be considered.

30. Denig, R.: Ueber der Häufigkeit der Localtuberkulose des Auges, Arch. f. Augenh. **31**:359, 1895.

31. Harman, N. B., in Kelynack, T. N.: Tuberculosis in Infancy and Children, New York, William Wood & Company, 1908, pp. 130-132.

32. Wilson, R. P.: Tuberculosis of the Eyeball and Adnexa in Egypt, Mem. Ophthalmic Lab., Giza, Ann. Rep., 1929, p. 46.

33. Rohrschneider, W., and Reiners, H.: Die Bewertung des Lungenbefundes bei tuberkuloseverdächtigen Augenkrankheiten, Klin. Monatsbl. f. Augenh. **96**:778, 1936.

34. Marchesani, O.: In welchem Umfange darf bei Erkrankungen des Auges tuberkulöse Aetiologie heute als sichergestellt gelten? Klin. Wchnschr. **11**:1921, 1932.

In the United States, Goldenburg and Fabricant,[35] in a paper read before the section of ophthalmology of the Americal Medical Association based on the observation of 1,073 sanatorium patients with proved tuberculosis, reported that 7 patients had pathologic changes in the iris, a percentage of 0.67, of which the lesions of only 3, or 0.27 per cent, could seriously be considered tuberculous. Examination of the fundus of 914 patients revealed deviation from the normal in 78, in only 19 of whom, or 2.08 per cent, the condition could possibly be considered tuberculous. Of these 19 patients, 18 had unilateral involvement, an occurrence which would exclude the infection by toxin.

In a paper read before the section of ophthalmology of the New York Academy of Medicine, Eggston,[36] came to the following conclusion:

> The ocular lesions frequently diagnosed as tuberculosis in a patient with positive reactions to tuberculin are really not due to infection by tuberculous bacteria, with the formation of a tubercle, but are of an allergic nature, if they are in any way related to tuberculosis. Actual tuberculous infection of the eye is relatively rare.
>
> Injections of tuberculin are of value in the allergic cases if given properly in order to desensitize the patient, but of questionable value in the active tuberculous ones.

Five years of experience with tuberculous patients in the Atlantic County Hospital for tuberculosis has led me to similar conclusions. I have encountered no anomalies of the eye which I could definitely ascribe to pulmonary infection. The most common complaints were fatigue, tenderness, burning sensations in the eyes and, frequently, supraorbital pain, symptoms generally due to refractive errors and muscular asthenopia, which are more common among patients who are confined to bed and read a good deal under unfavorable conditions. Another patient, with a history of head injury, sustained several years previously, had diplopia. A patient with plastic iritis of questionable origin also exhibited a positive Wassermann reaction. Another patient had atrophy of one nerve head, the cause of which was not clear. Peter[36a] found no uveal lesions in 300 cases of the last stages of pulmonary tuberculosis.

Woods[37] stated that the diagnosis of ocular tuberculosis must be based on the course and character of the lesion, on the exclusion of other etiologic factors and on a study of the general tuberculous status of the patient. Reactions to tuberculin are of value only when strongly positive. Weakly positive or negative reactions are of no significance for or against the diagnosis of ocular tuberculosis. Even when nodules are noted in the iris or choroid, some authors question their tuberculous origin. Kapuscinski[38] of Posen, Poland, reported a case of iridocyclitis with "tuberculous" nodules on the iris of each eye. However, all the clinical tests for tuberculosis, including injections of tuberculin in doses up to 25 mg., as well as inoculation of material from the nodule in a guinea pig and a rabbit, gave completely negative reactions. After reviewing the literature on the subject, the author concluded that the problem of ocular tuberculosis deserves a more critical consideration than has generally been given it.

On the other hand, 365 patients with ocular tuberculosis were reported by Mehlmack[39] from Hertel's clinic, in Leipzig. The largest number of patients were between 20 and 50 years of age. The majority of the patients—between the twentieth and the thirtieth year of life—were women. The uveal tract was the seat of the disease in 80 per cent of patients. In practically all the patients with uveal tuberculosis primary lesions were observed in the chest. The tuberculin reaction was positive in practically all the patients in whom clinical and roentgenographic examination revealed inactive tuberculosis, but in a number of the very young patients and in some of the women during the menopause the reaction was negative in spite of definite evidence of active generalized tuberculosis, such as involvement of the lymph glands, with or without pulmonary involvement. Stock[39a] contended that chronic inflammations of the eye and its adnexa, particularly chronic uveitis, are tuberculous in origin. Lagrange[39b] expressed a similar opinion.

Werdenberg[40] observed a notable parallelism between tuberculous lesions of the eye and those of the thorax:

> Ocular tuberculosis . . . is expressed by the presence of an ascending infection from the tuberculous hilar

35. Goldenburg, M., and Fabricant, N. D.: The Eye in the Tuberculous Patient, Arch. Ophth. **5**:66 (Jan.) 1931.

36. Eggston, A. A.: The Use of Tuberculin in Diagnosis and Treatment in Ophthalmology, Arch. Ophth. **8**:671 (Nov.) 1932.

36a. Peter, L. C.: Eye Phenomena Observed in 300 Cases of Pulmonary Tuberculosis, Am. J. Ophth. **33**: 105, 1916.

37. Woods, A. C.: Problem of Ocular Tuberculosis, Am. J. Ophth. **21**:366, 1938.

38. Kapuscinski, W.: Ocular Tuberculosis, Arch. Ophth. **22**:934 (Nov.) 1939.

39. Mehlmack, F.: Zur Klinik der Augentuberkulose, Arch. f. Augenh. **110**:39, 1936.

39a. Stock, W.: Tuberkulose als Aetiologie der chronischen Entzündungen des Auges und seiner Adnexe besonders der chronischen Uveitis, Arch. f. Ophth. **66**: 1, 1907.

39b. Lagrange, H.: La tuberculose du tractus uvéal, Paris, G. Doin, 1923.

40. Werdenberg, E.: Typischer und atypischer Krankheitsverlauf bei Augentuberkulose, Klin. Monatsbl. f. Augenh. **85**:98, 1930.

glands. . . . One must bear in mind that mild and severe forms of this mediastinal disease may give rise to equally malignant tuberculous lesions in the eyes. Often the roentgenogram fails to reveal the source of the disease; nevertheless, in the presence of a malignant intraocular process, one must infer that a similarly malignant tuberculous condition is active elsewhere in the body. Finnoff,[40a] in his studies of ocular tuberculosis, concluded that chronic uveitis is frequently tuberculous. The tubercle bacilli enter the eye from known or unknown foci through the blood. In most cases tuberculous uveitis is characterized by nodules. No part of the uvea is invulnerable. Obscure chronic inflammation is often due to tubercle bacilli, except for that of the conjunctiva and cornea. In most cases the foci are relatively inactive and are often impossible to locate with present methods of examination.

Urbanek[41] came to similar conclusions. In a large number of cases of ocular disease diagnosed as tuberculous uveitis and other inflammatory conditions, roentgenographic examination revealed that the lungs were not normal. Tuberculosis in the lungs most frequently associated with ocular disease is of the mildest type and presents few symptoms or physical signs. The tubercle bacilli in cases of this type seem to lack the ability to produce the typical granulation tissue with central caseation, or even characteristic giant cells. Urbanek claimed that he noted the tubercle bacilli in the blood stream of patients suffering from episcleritis and sclerosing keratitis. He expressed the opinion that the hypodermic injection of preparations of tuberculin is the best method of diagnosis. The allergic reaction of the patient to the tuberculin antigen must be carefully noted. Administration of the test to about 100 adults with scrofulous keratoconjunctivitis proved that the majority reacted positively. Arnold Knapp, in 1 case, obtained by culture a tubercle bacillus from the aqueous in a case of iridocyclitis with sclerosing keratitis.

Krasso[42] stated:

> It is common knowledge that a disease of the eye may be of tuberculous origin even though the histologic examination shows no typical tuberculoma. With definite evidence of a tuberculous origin the involvement in question may display a nonspecific simple inflammatory reaction. In the etiologic diagnosis of tuberculosis of the eye one should make a diagnosis . . . in addition to bacillary and histologic investigations.

Lloyd[43] went so far as to say that most of the so-called focal infections of the eye are really tuberculous. Relapses, he stated, are due to periods of lowered resistance. He stated the opinion that intraocular hemorrhage in young persons is of tuberculous origin unless proved otherwise.

Other observers even offered the opinion that a tuberculous origin may be assigned to all obscure ocular conditions. Pillat,[44] for example, observed that the list of ocular diseases which are considered tuberculous in the absence of a positive reaction to tuberculin may be extended. The ophthalmologist cannot reject a tuberculous cause because of a negative Pirquet or Mantoux reaction. One must remember that there are tuberculous diseases in which the Mantoux reaction is negative but the reaction to Moro's tuberculin in an ointment base is positive, and, further, that the Mantoux reaction, although negative for forty-eight hours, may become positive in eight days.

A school headed by Löwenstein[45] and Meller,[46] of Vienna, maintained that tuberculosis not only is the cause of ocular disease in which tubercles can be demonstrated but may be the etiologic factor in a host of ocular inflammatory processes of doubtful character, especially those of a recurrent or chronic type, even though a tuberculous origin cannot be demonstrated elsewhere. Fontana[47] asserted that "focal infection," a favorite etiologic factor with oculists a generation ago, was in reality tuberculous in nature.

Fontana's allusion to focal infection brings to mind a similar controversy with reference to the cause of obscure chronic ocular diseases. After Lang[48] (1913) made known his observations on the influence of dental sepsis on diseases of the eye, the effect of infected teeth on the eye was seriously discussed by members of the medical profession. It was shown that, aside from the structural proximity to and the anatomic relation of the visual organ to the teeth, there was a special selectivity of the

40a. Finnoff, W. C.: Ocular Tuberculosis, Arch. Ophth. **53**:130, 1924; Tuberculosis in the Etiology of Acute Iritis, Am. J. Ophth. **14**:127, 1931; Relation of Tuberculosis to Chronic Uveitis, ibid. **14**:1208, 1931.

41. Urbanek, J.: Ocular Tuberculosis, Tr. Ophth. Soc. U. Kingdom **52**:227, 1932. Urbanek, J., and Meller: Tubercle Bacilli in Blood in Diseases of the Eye, Arch. Ophth. **4**:262 (Aug.) 1930.

42. Krassó, J.: Diagnosis of Tuberculous Diseases of the Eye and Their Treatment with Subconjunctival Injections of Virulent Human Tubercle Bacilli, Orvosképzés **25**:267, 1935; abstracted, Arch. Ophth. **17**:1145 (June) 1937.

43. Lloyd, R. I.: Tuberculosis of the Eye, Am. J. Ophth. **13**:753, 1930.

44. Pillat, A., in discussion on papers by Krückmann, Rohrschneider and Volkel, Arch. Ophth. **23**:420 (Feb.) 1940.

45. Löwenstein, E.: Das Vorkommen der Tuberkelbazillämie bei verscheidenen Krankheiten, München. med. Wchnschr. **78**:261, 1931.

46. Meller, J.: Tub. bacil. in das Blut des kranke Auge, Ztschr. f. Augenh. **13**:41, 1930.

47. Fontana, G.: Ricerche citologiche sul sangue di individui affetti da congiuntivite flittenulare, Boll. d'ocul. **11**:582, 1932.

48. Lang, W.: The Influence of Chronic Sepsis upon Eye Diseases, Lancet **1**:1368, 1913.

micro-organisms and toxins of dental disease for ocular tissues. Rosenow,[49] of the Mayo Clinic, demonstrated that when bacteria are taken from diseased teeth and injected in the blood stream of animals, they produce diseases of the eye and that, within limitations, this selectivity is characteristic of the bacterial strain and is manifested through several cultural transplants of the organism. Zanettin[50] produced plastic iridocyclitis in animals by injecting a strain of the streptococcus from a suspected tooth of a person with iridocyclitis.

Older ophthalmologists well remember how frequently patients were deprived of their teeth on the mere supposition that the ocular lesion was caused by dental caries or pyorrhea. Lang's dictum that "it is better to lose thirty-two teeth than one eye" was taken as justification for wholesale extraction of teeth. All arguments that only a small proportion of patients with dental disease suffer from ocular complications, and that the larger number of patients with pyorrhea and alveolar abscesses applying for dental treatment have no ocular lesions were of no avail. The fact that the removal of a septic tooth does occasionally result in clearing up of a chronic inflammatory condition of the eye was sufficient to lead some workers to ascribe all such obscure chronic lesions to dental sepsis. No consideration was given to the fact that for each case of cure by dental extraction reported, many cases in which the treatment was unsuccessful have never been made public. The argument against dental sepsis as an etiologic factor in all ocular disease may be applied with more force to tuberculosis, even in cases in which tuberculous lesions have been detected elsewhere in the body.

While uveal tuberculosis is frequently difficult to diagnose, tuberculosis of the external segment of the eye in most instances may be ascertained by laboratory investigation. Eyre[51] studied 206 patients with tuberculous conjunctivitis, for all of whom the diagnosis was based on the presence of the bacillus in the conjunctival sac and on reproduction of the disease in animals by means of inoculation. In 46 patients he observed ulcerations of the conjunctiva; in 25, miliary tubercles; in 80, hypertrophic granulations; in 46, lupus, and in 9, pedunculated tumors. Of 2,500 patients with ophthalmic disease in London hospitals, he saw only 8 with tuberculous conjunctivitis. As to the method of invasion, he expressed the belief that the disease is secondary to nasolaryngeal tuberculosis. Frequently a slight trauma or breaking down of a phlyctenule furnishes a nidus for the growth of the bacilli.

Eyre did not agree with Arlt, who was first to express the opinion that tuberculous conjunctivitis is caused by the spread of the disease from the face. Arlt based his opinion on a case of tuberculous conjunctivitis encountered in 1864, in which the disease was produced by the spread of lupus. Lundsgaard[52] expressed the opinion that tuberculous conjunctivitis is an endogenous infection and differs from lupus, which is ectogenous. These two lesions, according to Lundsgaard, differ also with respect to the age incidence. Conjunctival tuberculosis affects persons under 20, while lupus occurs in adults up to 52 years of age. Tuberculous conjunctivitis, also, is always unilateral and is more severe than lupus, involving the upper lid and the periocular glands, and is often associated with swelling and abscess formation.

Tuberculous conjunctivitis is a disease characterized by the presence of one or more ulcers, which are covered with necrotic, dirty gray material, through which loops of granulation tissue protrude. The ulcers spread slowly, with little disposition to heal. The lesions appear usually in the tarsal conjunctiva. The lymph glands become swollen, the glandular involvement being followed by swelling of the glands of the lower jaw and the neck; the glands, however, are not the primary source of infection, as they may be with tuberculous uveitis. According to this description, tuberculous conjunctivitis is a primary disease of serious consequence.

In Egypt, according to Wilson,[32] the tubercle bacilli seem to have a special predilection for the conjunctival membrane; the incidence of tuberculous conjunctivitis is one-third that of all forms of tuberculosis. The disease plays a more important part in the causation of lesions of the cornea than is usually admitted. According to Wilson, tuberculous conjunctivitis is essentially a disease of early life. Histologically the ocular lesions do not differ from tuberculous

49. Rosenow, E. C.: Iritis and Other Ocular Lesions on Intravenous Injection of Streptococci, J. Infect. Dis. **17**:403, 1915.

50. Zanettin, G.: Infezioni focali e malattie oculari, Ann. di ottal. e clin. ocul. **62**:588, 695 and 786, 1934.

51. Eyre, cited by McKee, S. H., in Berens, C.: The Eye and Its Diseases, Philadelphia, W. B. Saunders Company, 1936, pp. 407-408.

52. Lundsgaard, K. K. K.: Tuberculosis Conjunctivae: Eventual Fate of the Patients, Acta ophth. **1**:39, 1923; cited by Blegvad, O.: Die Konjunktivaltuberkulose, ibid. **11**:345, 1933. J. M. Ball, many years ago, demonstrated that lupus attacks the conjunctiva, that over 50 per cent of cases of tuberculosis of the conjunctiva are due to lupus (Modern Ophthalmology, ed. 3, Philadelphia, F. A. Davis Company, 1913, p. 289).

foci seen in other parts of the body. In many cases granular conjunctivitis is in reality tuberculosis of the conjunctiva. Haab described a case of trachoma which on closer examination proved to be of tuberculous origin.

Benalioua [53] stated the opinion that primary tuberculous infection of the conjunctiva, long considered grave, has in reality a favorable prognosis, cures occurring without any complication except bacillary migrations, which are without danger, the bacilli no doubt being conveyed by an erythema. The disease is one of children and young adults and is seen more frequently in females than in males. It is unilateral and sluggish and is associated with various lesions of the mucous membrane, and frequently with numerous caseous glands. The author expressed the belief that the treatment should not be too aggressive and should be systemic. This favorable prognosis applies particularly to the phlyctenular form of conjunctivitis.

Phlyctenulosis, derived from the Greek word φλυκταινα, meaning a "blister," is really a misnomer, since the lesion from its very beginning, is not a blister, but a pustule, which quickly breaks down to form an ulcer.

Because phlyctenulosis is frequently associated with eczema, the term "eczematous conjunctivitis" was used to designate this conjunctival disease. Older authors, such as Scarpa and Mackenzie, used the term "scrofulous ophthalmia" to describe phlyctenular disease of the eye. Scrofulous conjunctivitis or keratitis is still a favorite term among some authors, since the disease has a tendency to involve the glands. It is the most common ocular disease among the children of Europe.

In China, Wang [54] studied its occurrence in Shanghai; of 4,292 patients treated in the clinic in 1931, 819, or 19.1 per cent, were scrofulous. The highest incidence was between April and July. Wang stated that weather and living conditions were the direct cause of the high incidence of scrofulous disease in China during these months. More men than women were affected, and the disease was more common in adults than in children. Wang found that 92 per cent of his patients responded to the Mantoux test. He stated that phlyctenulosis has a nonspecific anaphylactic basis in persons with tuberculous diathesis.

Leber [55] was first to state that phlyctenular disease of the eye is caused by tuberculous toxins reaching the eye through the blood stream, apart from the bacilli themselves. He based his opinion as to the tuberculous nature of the conjunctival disturbance on the occasional occurrence of crops of phlyctenules after the injection of tuberculin.

Evidence supporting the relation of phlyctenular disease to tuberculosis has since been produced by Weekers [56] and Loddoni.[57] They demonstrated that phlyctenulosis may be produced by instillation of tuberculin in the conjunctival sac of persons who are hypersensitive to the tubercle bacillus. It may also be produced in animals which are hypersensitive to foreign protein, horse serum, for example, by instillation of such a substance in the conjunctival sac. They admitted, however, that other substances may quite possibly be responsible for phlyctenulosis in certain persons.

Ajo,[58] of the Ophthalmic Clinic at the University of Helsingfors, Finland, observed 367 patients, of a total of 449 with phlyctenular disease, in a period of fifteen years (1912-1927). Tuberculosis was the cause of death in 35 of the 55 fatalities and was the probable cause of death of 4 other patients, the mortality rate for tuberculosis being thus 10.62 per cent. Of the 100 living patients still under his care at the end of the experiment, 50 were free from the disease. Of the remaining 50, 39 showed tuberculous changes; 5, changes which were probably tuberculous, and 6, other pathologic changes. Pulmonary tuberculosis was observed in 7 patients. Ajo expressed the opinion that patients with phlyctenular disease may have a severe form of tuberculosis later in life.

Giannantoni and Possenti [59] studied 150 patients with clinical and roentgenologic signs of pulmonary tuberculosis. The ages of the majority ranged from 20 to 50, phlyctenular conjunctivitis occurring in 22.66 per cent and follicular hypertrophy in 30 per cent of the patients. Sties, chalazion and blepharitis were

53. Benalioua: La primo-infection tuberculeuse de la conjunctive, Ann. d'ocul. **175**:746, 1938; abstracted, Arch. Ophth. **21**:877 (May) 1939.

54. Wang, C. L.: Zur Statistik und Pathologie der skrofulösen Augenentzündungen in Shanghai, Klin. Monatsbl. f. Augenh. **93**:505, 1934.

55. Leber, T.: Arch. f. Ophth. **3**:251, 1884; cited by Duke-Elder, W. S.: Textbook of Ophthalmology, St. Louis, C. V. Mosby Company, 1941, vol. 3, p. 2318.

56. Weekers, L.: Phlyctènes oculaires et tuberculose, Arch. d'opht. **44**:342 and 411, 1927; L'anatomie pathologique des phlyctènes oculaires, Bull. Acad. roy. de méd. de Belgique **24**:435, 1910.

57. Loddoni, G.: Cherato-congiuntivite flittenulare e allergia, Ann. di ottal. e clin. ocul. **58**:28, 1930.

58. Ajo, A.: Zur Frage des späteren Schicksals der Phlyktänulosepatienten mit besonderer Berücksichtigung der Tuberkulose, Acta ophth., 1938, supp. 15, p. 1.

59. Giannantoni, C., and Possenti, G.: Sintomi oculari nella tubercolosi polmonare, Ann. di ottal. e clin. ocul. **61**:823, 1933.

frequent among the younger patients. The authors also observed primary lesions in the chest in 80 per cent of the patients with disease of the uveal tract.

Fontana [47] observed tuberculosis in the lungs in 50 per cent of cases of phlyctenular conjunctivitis. He concluded that there is a close association between phlyctenular conjunctivitis and tuberculosis. This opinion was shared by Riehm, who stated that phlyctenular keratoconjunctivitis for the most part, particularly in Europe, has tuberculosis as the basic cause.

In England, Harman's observations on phlyctenular conjunctivitis showed that the disease was benign, and not of tuberculous origin. He stated [60]:

> The records show that disease occurs during the fourth to the seventh year, with maximum incidence in the fifth year. It is a disease of the poor and ill fed. In Belgrave Hospital for children, during a period of ten years, one half of the children were cured in one week; three fourths were well in a fortnight; and all except a small group of three per cent, who developed severe keratitis, were cured by the sixth week.

The contents of the phlyctenules were examined in 23 cases. In 21 cases they proved to be sterile. Harman concluded that the phlyctenulosis was a herpetiform eruption produced by chronic irritation of the collateral branches of the fifth nerve in debilitated children and that it had no essential relation to the tubercle.

Harman significantly remarked [60]:

> . . . no one would hesitate to acknowledge that phlyctenular conjunctivitis would be likely to appear in tuberculous disease, even as it does in those who are ill-fed and debilitated, but I think the evidence indicates that the direct exciting cause is the irritation of the fifth nerve by nasal and oral sepsis in these weakened children.

With respect to tuberculosis of the interior portion of the uvea—the iris, the ciliary body and the choroid—the inflammation of the iris can easily be seen. The inflammatory process of the ciliary body in tuberculous ocular infection is sufficiently distinct to be diagnosed, particularly when the changes are of long duration and are gross. The evidences of tuberculosis of the choroid, however, are not apparent until after removal of the eye.

Nias and Paton [61] (1906), in a study of a series of cases of phlyctenular conjunctivitis, observed that the opsonic indexes to the tubercle bacillus were practically normal; no tuberculous lesions in the body were demonstrable in these cases.

Tejeda [62] studied 100 cases of phlyctenular ophthalmia with respect to the relation of the disease to tuberculosis, the history, the clinical symptoms, the reaction to tuberculin and the roentgenographic evidence being considered. After reviewing the histories, the author concluded that the relation between phlyctenular conjunctivitis and tuberculosis was not established. He found a positive reaction to tuberculin in 86 cases. In his opinion, the great frequency of a positive tuberculin reaction in cases of phylctenular conjunctivitis is not conclusive evidence of any relation to tuberculosis.

The predominant opinion of American observers is that this disease bears little relation to tuberculosis. The fact that phlyctenular conjunctivitis has greatly decreased with the improvement of living conditions, better dietary standards and administration of vitamins adds weight to the belief that the disease is the result of faulty metabolism.

The relation of phlyctenulosis to the enlargement of the glands of the neck led many authors to the belief that ocular disease is associated with tuberculosis of the glands rather than with tuberculosis of the lung. Werdenberg,[63] in a study of 500 patients, detected mild tuberculosis of the glands in 60 per cent, roentgenographic evidence, without clinical signs of tuberculosis of the lung, in 30 per cent and clinical pulmonary disease in 10 per cent. From these observations, he concluded that the mode of infection of the eyes is not by flooding of the blood stream with a large number of bacilli but, rather, by slow passage of a small number of bacilli from a quiescent focus to the ocular tissues. Grönholm,[64] in a study of 100 patients with ocular tuberculosis, observed that 55 per cent had infected glands and 18 per cent tuberculosis of the lungs.

Because involvement of the glands has been noted in most patients with scrofulous ophthalmia, the opinion has been expressed by many observers that phlyctenular disease frequently noted in children is an early symptom of tuberculosis. Völkel,[65] of Freiburg, observed 12 allegedly tuberculous children in an institution. Seven presented evidence of exudative lymphatic diathesis. These children had hypertrophic pharyngeal and palatine tonsils, palpable cervical

60. Harman,[31] pp. 130-142.

61. Nias, J. B., and Paton, L.: Contribution to Study of Phlyctenular Conjunctivitis, Tr. Ophth. Soc. U. Kingdom **26**:232, 1906.

62. Tejeda, M.: Conjunctivitis flictenular y tuberculosis, Arch. de oftal. hispano-am. **32**:219, 1932.

63. Werdenberg, E.: Neuere Gesichtspunkt zur Beurteilung und Behandlung der Augentuberkulose, Schweiz. med. Wchnschr. **59**:126, 1929.

64. Grönholm, V.: Ocular Tuberculosis and Constitution, Acta ophth. **6**:297, 1928.

65. Völkel, R.: Tuberculosis of the Eye in Children, Arch. Ophth. **23**:419 (Feb.) 1940.

glands, a tendency to eczema, large hilar glands, evident roentgenographically, and impaired physical condition. Two of the children suffered from general scrofula. In the patients with chronic recurrences, the condition in the eye paralleled the changes in the general condition. Recurrences, with simultaneous involvement of the affected cervical glands and joints, were said to be due to hematogenous dissemination.

In view of the variations in the laboratory data and the clinical reports, authors have tried to reconcile the apparently strange action of the tubercle bacilli. Gómez-Márquez,[66] for example, advanced the following theory:

> . . . in cases of early infection the functional defenses of the organism are increased, and not only is the bacillus overcome, but the patient is rendered immune and nonallergic. In other cases the tuberculous child also recovers from his first attack and is rendered immune, but his tissues have been sensitized, or rendered allergic, and new inoculations are followed by more or less violent inflammatory reactions, which vary according to their site and are not characteristic of tuberculosis. In still other cases the tuberculous child acquires only a partial immunity, with or without allergy. Later, if the number of bacilli attacking the child is small, he is able to resist the attack, but if the number is large, he is unable to resist the invasion, and typical tuberculous lesions make their appearance in the organs in which the inoculations take place. Among the ocular lesions of this class is parenchymatous keratitis, which is tuberculous as often as syphilitic.
>
> In the diagnosis of atypical tuberculosis, in cases in which it is impossible to find tubercle bacilli or the primary focus of infection, and in which serodiagnosis, a seroprecipitation test, determination of the opsonic index and fixation tests all give positive results, a positive Pirquet or Mantoux reaction may simply indicate a state of allergy or relative immunity originating from the primary infection.

Rich and McCordock[67] expressed the opinion that the acute inflammatory reaction evidenced by the tuberculous animal is due to sensitization of the fixed cells to tuberculoprotein and is of an allergic nature. They expressed the resulting tuberculous lesion by the following formula

$$\text{Lesion} = \frac{\text{Virulence} \times \text{number} \times \text{degree of allergy}}{\text{Resistance}}$$

If the virulence and number of the invading organisms are great, the degree of allergy is high and the resistance of the patient is low, a spreading, necrotizing inflammatory reaction results. On the other hand, if the resistance of the patient is high, the virulence and number of bacilli are low and the degree of allergy is slight, a mild lesion will result.

Werdenberg and Samoilov[68] divided ocular tuberculosis into two types: (1) a "mild, productive or productive-fibrous" lesion, which tends to heal and occurs either in the stage of primary infection or in the third stage of high resistance, and (2) a "hypersensitive, chiefly exudative" type.

Urbanek[41] introduced the following classification of tuberculin sensitivity in cases of ocular tuberculosis: 1. A person who is free from tuberculosis, has never had the disease and shows no reaction to large intracutaneous injections of tuberculin or tebeprotin is said to be in a state of anergia. 2. If a healthy person is infected, the organism tends to produce antibodies, as shown by tuberculin sensitivity, or allergy. (*a*) If the course of the disease is favorable, the allergy becomes stronger as the antibodies increase, and very small doses of tebeprotin cause a positive reaction. (*b*) When the tubercles become encapsulated and bacilli disappear from the rest of the body, the degree of allergy diminishes and, with complete healing, is changed into a positive anergia, the result of destruction of bacteria. (*c*) In cases of severe disease the original allergy becomes progressively weaker, with an increase in toxin and a decrease in formation of antibodies, until the latter completely ceases and a negative anergia is present, the result of the complete destruction of all the defensive powers of the organism. In this state death may result from injection of the tuberculin.

Woods[69] stated that allergy and immunity influence to a high degree the type of lesion which results from infection of the tubercle bacilli. When the normal animal is inoculated with tubercle bacilli, it shows a progressive, sluggish development of generalized tuberculosis, with formation of tubercles. When the tuberculous animal is so inoculated, an acute inflammatory reaction, with caseation and necrosis, results. In persons with high resistance and a low degree of allergy, tubercle bacilli lodging in the eye apparently cause lesions which are nonspecific in their appearance and have a tendency to become circumscribed and to heal. On the other hand, if the patient has low resistance and a high degree of allergy, the tendency is toward inflammatory lesions of a

66. Gómez-Márquez, J.: Tuberculosis oculares típicas y atípicas, Arch. de oftal. hispano-am. **30**:17, 1930.

67. Rich, A. R., and McCordock, H. A.: Enquiry Concerning Role of Allergy, Immunity and Other Factors of Importance in Pathogenesis of Human Tuberculosis, Bull. Johns Hopkins Hosp. **44**:273, 1929.

68. Werdenberg, E.: Die Augentuberkulose im Licht der neuen Tuberkuloseforschung, Klin. Monatsbl. f. Augenh. **75**:546, 1925. Samoilov, A. J.: Principles of Specific Therapy in the Tuberculous Diseases of the Eye, Russk. ophth. j. **12**:145, 1930.

69. Woods, A. C., in Berens, C.: The Eye and Its Diseases, Philadelphia, W. B. Saunders Company, 1936, p. 1183.

spreading, necrotizing type. Also, if the number and virulence of the organism are great, lesions, such as tuberculoma of the anterior or the posterior portion of the uveal tract, will result, with a pronounced inflammatory reaction and a tendency to spread, caseate and ultimately perforate the eyeball. These are the characteristics of tuberculous lesions.

SUMMARY AND CONCLUSION

From the varied opinions cited, it is evident that the relation of ocular tuberculosis to tuberculosis of other organs, particularly the pulmonary form, has not been definitely established. The positive reaction to the Pirquet or Mantoux test can no more serve as evidence on which to ascribe chronic ocular lesions of an obscure nature to tuberculosis of some other organ of the body than can the positive Widal reaction account for all complications of typhoid. A favorable response to the tuberculin test, likewise, is no proof of the diagnosis; other foreign proteins may equally well ameliorate the ocular condition of certain patients, and all too often the conclusion is based on the fallacy of sequence of events—*post hoc, ergo propter hoc.*

Before tuberculin was brought to the attention of the medical profession, the diagnosis of tuberculosis of the eye was based on the presence of a similar condition elsewhere in the body. The diagnosis was established in much the same way as is syphilitic infection of the eyes, namely, on the basis of a clinical and laboratory report of syphilis. When tuberculin came into use, its diagnostic value became of permanent importance. The diagnosis of tuberculosis was based on a positive reaction. Later, when it was shown that the intradermal test with tuberculin was not infallible, arguments in its defense appeared in the ophthalmologic literature.

A generation ago focal infection was accepted as an etiologic factor in obscure ocular disease. Later endocrinopathy was hailed as an explanation of morbid conditions of uncertain origin. Now allergy is being stretched to the limits as an etiologic factor in many ocular complications the cause of which cannot be detected by the usual scientific methods. One theory after another has been advanced to show the diagnostic merits of tuberculin, none of which, however, have fitted into the scheme of the etiologic diagnosis of all obscure diseases of the eye. The fact remains that the eye appears to possess an immunity against active pulmonary tuberculosis, and a positive reaction to tuberculin does not indicate where the lesion is located.

Formerly, ocular lesions of doubtful origin were designated as idiopathic—a frank confession that the cause was not known. In this scientific age one must have a cause for everything, any kind of a cause, even if it is unscientifically conceived. This inability to say "I don't know" appears to be the most regrettable trait of modern medicine, and this is peculiarly true with respect to ocular tuberculosis.

From the literature cited, certain facts are evident: 1. Phlyctenular keratoconjunctivitis is not usually of tuberculous origin. 2. Tuberculous lesions of the eye are not nearly as common as they are generally supposed. 3. Uveal tuberculosis is not necessarily seconday to tuberculosis elsewhere in the body. The fact that the ocular tuberculosis frequently leaves the lungs undamaged shows that the tubercle bacillus may enter the blood stream and attack the eye directly. 4. The nature of an infection in the anterior segment should always be determined in the laboratory. When it is impossible to obtain a specimen of the uveal tissue, a provisional diagnosis may be made by microscopic study of the lesion, by the general tuberculous status of the patient and by exclusion of other etiologic factors. Tuberculin tests are of value only when associated with other features of the case.

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Obituaries

CARL HAMBURGER

1870-1944

Dr. Carl Hamburger, who died in May 1944, was born in 1870. He graduated in 1893 and spent several years in general hospital service and in the ophthalmic clinic of Hirschberg, in Berlin. It was during this period that he carried on investigations under Ehrlich.

In 1898 he settled in Berlin as oculist and gave evidence of his earnest investigations on the physiology of the eye in the publication, between 1898 and 1925, of studies on the source of the aqueous humor. He also published the results of early investigations on such subjects as the nutrition of the eyeball and tonometry. His interests were wide, and his writings, which were extensive, were not limited to ophthalmology. He was deeply interested in hygiene, not only in ocular but in communal hygiene; and in these fields, too, his contributions were numerous and valuable. His clinical studies were many and chiefly devoted to glaucoma, and his contributions concerning the therapeutic value of epinephrine for glaucoma are well known.

Dr. Hamburger was an interesting personality. His scientific interests were deep and intensive.

His wife was the daughter of the celebrated oculist Herman Cohn, of Breslau, and the sister of the well known writer Emil Ludwig.

Dr. Hamburger gave distinguished service as medical officer in the German army from 1914 to 1919. His reward was the Iron Cross—and later exile, at the age of 69. He and his wife found refuge in Geneva, Switzerland, where he continued some studies. He died at Gland, near Geneva, his wife having preceded him in death by two years.

The sorrow and tragedy of this outstanding ophthalmologist are not lessened by the fact that he is but one of many.

HARRY FRIEDENWALD.

Correspondence

VERNAL CONJUNCTIVITIS

To the Editor:—Luis Castellanos A., of Chihuahua, Mexico, published a fascinating article entitled "Ariboflavinosis as a Probable Cause of Vernal Conjunctivitis" in the March issue (ARCH. OPHTH. **31:** 214, 1944). I disagree with the author's theory, which lacks scientific confirmation.

I am amazed that Dr. Castellanos has made no mention of vernal conjunctivitis as an ocular manifestation of an allergic state. The literature is replete with experimental evidence of its allergic origin. The clinical symptoms of the disease have been produced out of season by inserting in the conjunctival cul-de-sac pollens to which the patient was shown to be sensitive by intradermal tests during seasonal attacks.

The periodicity of vernal conjunctivitis in correspondence with the pollenation of the trees, grasses and weeds is no more coincidental than the onset of autumnal hay fever, which begins on or about August 15. The approach of warm weather in April coincides with the first appearance of symptoms of itching, lacrimation, redness and mucous discharge. In cases appearing for the first time in midsummer or late summer mild symptoms have been present for weeks, becoming intensified with the heat and humidity, so that the patient seeks medical relief. Prompt relief of symptoms by the use of epinephrine or epinephrine-like products is characteristic of allergic manifestations. The high incidence of positive reactions obtained by intracutaneous tests also corresponds with the incidence of such reactions obtained with other allergic manifestations. The local eosinophilia and the eosinophilia of the blood are common with vernal conjunctivitis, as they are with other forms of allergy.

It seems hardly necessary to verify a point that has already been proved beyond doubt. This becomes necessary, however, when the ARCHIVES gives conspicuous space to an article purporting to refute a recognized fact. The description of vernal conjunctivitis by Dr. Castellanos certainly differs from that which I had already published in the ARCHIVES (Lehrfeld, L.: Observations on Eighty-Seven Cases at the Wills Hosptial [1929-1931], ARCH. OPHTH. **8:** 389 [Sept.] 1932; Lehrfeld, L., and Miller, J.:

Additional Research on Vernal Conjunctivitis, ibid. **21:** 639 [April] 1939). Dr. Castellanos does not differentiate between the limbal and the palpebral type of the disease. The former is seen largely in the Negro race in this part of the country and appears only in the spring and late summer, disappearing completely in the fall and winter. The palpebral type is described as (1) follicular conjunctivitis, (2) cobblestone conjunctivitis and (3) giant granuloma.

These three forms represent degrees in the chronicity of the disease, the first developing into the second and the second into the third, the stage depending on the duration of the disease. It is likely that the difference in Dr. Castellanos' description is explained by a difference in the disease in Mexico.

There is a wide gap between the suggestion that vernal conjunctivitis is associated with ariboflavinosis and scientific proof to substantiate the theory. Dr. Castellanos fails to offer any data on the levels of riboflavin in the urine in patients under his care. Bulletin No. 109 of the National Research Council, entitled "Inadequate Diets and Nutritional Deficiencies in the United States," published in November 1943, states that riboflavin deficiencies can be determined by urinalysis.

My Mexican fellow ophthalmologist states that he obtained immediate improvement in 92 per cent of his patients after the use of riboflavin. He asserts that 35 patients showed immediate improvement on the third or fourth day and that 62 patients showed improvement in ten to fifteen days. There was no report of an actual cure. This experience differs from the observation of many investigators that a much greater time is needed for the relief of ariboflavinosis.

With regard to the use of riboflavin, I quote from the bulletin of the National Research Council:

> . . . Several investigators have used corneal vascularity as an index of riboflavin deficiency in surveys of population groups. Its validity for this purpose has been questioned, for many consider that it is not yet confirmed that all, or nearly all, of these vascular changes are due only to riboflavin deficiency or that they are a necessary accompaniment of other undoubted signs of riboflavin deficiency. The consensus of this group at the present time seems to be that one cannot assume that all significant degrees of corneal vascularization are due to riboflavin deficiency. Sandstead, following riboflavin therapy for 60 to 110 days, found no significant change in corneal vascularity which could be ascribed to this therapy; it seems doubtful that superficial vascularization of the cornea, as observed in this study and as found in the general population, should be considered a diagnostic sign of riboflavin deficiency. . . . Youmans and Patton have observed a considerable number of subjects with mild but definite corneal vascularization not accompanied by ocular symptoms and in whom there was no correlation with dietary intake of riboflavin, other dietary factors or other evidence of deficiency disease. Reexamination of these subjects showed an improvement or disappearance of the vascularization in the winter or spring season compared with the fall, in spite of a lower intake of riboflavin in the former period.
>
> . . . It has been reported that recession of the lesions of chronic ariboflavinosis is very slow and is complete only after a very long period of time.

I wish especially to call to the attention of Dr. Castellanos and the readers of the ARCHIVES that the relief of ariboflavinosis is very slow, and is not as prompt as Dr. Castellanos has reported in patients with vernal conjunctivitis, namely, in a few days. The experience of investigators proves that a deficiency of riboflavin is most common in winter and least common in summer, whereas vernal conjunctivitis is a summer disease. Never has the onset of the disease been noted in the winter. The pathologic process of the type involving the lids may carry over until winter. Despite these facts, Dr. Castellanos speaks of a vitamin deficiency in the hot season, but does not prove his point.

I wonder whether the "improvement" which the author reported was not due to his local treatment, rather than to use of the riboflavin.

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Abstracts from Current Literature

EDITED BY DR. WILLIAM ZENTMAYER

Cornea and Sclera

EPIDEMIC KERATOCONJUNCTIVITIS FROM A SUBJECTIVE VIEWPOINT. T. D. ALLEN, Am. J. Ophth. **27:** 16 (Jan.) 1944.

Allen described interestingly his own case of keratoconjunctivitis. He concludes that from the subjective standpoint boric acid compresses, intravenous administration of vitamin C and encouragement were the most helpful therapeutic factors.

W. S. REESE.

Experimental Pathology

A COMPARISON OF THE OCULAR REACTIONS OF PIGMENTED AND ALBINO RABBITS TO NORMAL HORSE SERUM. T. F. SCHLAEGEL JR., Am. J. Ophth. **27:** 137 (Feb.) 1944.

After stating the purpose of his report and describing the procedure and results, Schlaegel draws the following conclusions:

"1. Gross and microscopic ocular reactions were essentially equal in pigmented and albino rabbits.

"2. The allergic mechanism of intraocular followed by intravenous injection of normal horse serum is less effective in producing gross and microscopic results than the method of sensitization by intradermal injection prior to injection made into the right eye.

"3. Gross and microscopic reactions were most pronounced when the intravenous followed the intraocular injection by 14 days.

"4. The microscopic picture of the injected eyes of severe reactors bore a close resemblance to that of sympathetic ophthalmia. The uveal infiltration in the non-injected eyes was very slight but present in 40 percent of the cases."

W. S. REESE.

General

OCULAR FINDINGS IN FEEBLE-MINDED MALE CASTRATES. R. G. SCOBEE, Am. J. Ophth. **26:** 1289 (Dec.) 1943.

Scobee examined 17 male castrates before and after androgen therapy. He found convergence insufficiency prevalent among the feebleminded, and castrates showed a definite tendency to development of exophoria after such therapy.

W. S. REESE.

THE GEOGRAPHICAL DISTRIBUTION OF OCULAR INFECTIONS. C. WEISS, Am. J. Ophth. **27:** 175 (Feb.) 1944.

Weiss presents a table in which the most important infectious diseases of the eye are arranged according to broad geographic zones.

W. S. REESE.

Injuries

A STUDY OF MUSTARD-GAS LESIONS OF THE EYES OF RABBITS AND MEN. I. MANN and B. D. PULLINGER, Am. J. Ophth. **26:** 1253 (Dec.) 1943.

Mann and Pullinger draw the following conclusions:

"1. The clinical pathology of the lesion involving the limbus is similar in man and the rabbit.

"2. The reaction in man and the rabbit is dependent on the size of the dose and the anatomic situation. The effects of vapor and liquid are different only when the actual amount of mustard gas which soaks into the tissues is different; that is, the difference is quantitative only.

"3. The late keratitis in man is seen as a degenerative ulceration depending on the initial damage sustained by the limbus and cornea, and not on any continued action of mustard gas or any of its breakdown products.

"4. From 3 it follows that in the present state of our knowledge prophylaxis is likely to be much more important than treatment. It is very difficult to assess the value of treatment in man, since the dose of mustard gas received can never be known, and no two cases will be comparable. Two eyes of the same patient may be comparable although by no means always, even when the lesions are due to vapor."

W. S. REESE.

NONPENETRATING INJURIES OF THE EYE. Z. MARKELOVA, Vestnik oftal. **22:** 27, 1943.

The ratio of nonperforating to perforating injuries of the eye in hospital X was 58:42. The lid and the cornea were most frequently injured, while the sclera and the conjunctiva were rarely involved. Erosions of the cornea were observed in about 30 per cent of cases. Deep injuries of the cornea (70 per cent) were complicated by iritis or iridocyclitis, which required hospitalization until complete recovery. Injuries with fragments were predominant (94 per cent); next

in order were blind, penetrating and gunshot injuries. If the foreign body was in the soft tissues of the lid or muscle and did not cause inflammatory symptoms, it was left alone. In the case of blind and of penetrating injuries of the soft tissues edema of the tissue was frequently not present. Plastic operations had to be done in 14 of 57 cases. Cataract and retinal detachment were the more severe complications. Cataract extraction was done in cases without inflammatory signs; otherwise the patients were evacuated to rear hospitals.

O. SITCHEVSKA.

Neurology

INCLUSION BODIES AND LATE FATE OF GANGLION CELLS IN INFANTILE AMAUROTIC FAMILY IDIOCY. O. MARBURG, Arch. Neurol. & Psychiat. **49:** 708 (May) 1943.

Investigation of several cases of infantile amaurotic family idiocy has revealed the existence of inclusion bodies and severe secondary cell degeneration. The inclusion bodies are partly argentophilic and partly argentophobic, the reaction depending on the kind of fat which forms their basis. In cases in which inclusion bodies are present there are almost always myoclonic states.

Precipitations outside the cells are due to degeneration of axons. It cannot be definitely decided whether precipitations have their origin in the tissue fluid as well (Alzheimer and Sturmer).

The clinical signs in a case of infantile amaurotic family idiocy are due only in part to the well known cellular changes, which affect merely the vegetative, and not the functioning, portion (fibrils). Only when the functioning part also is affected do neurologic signs appear.

The atonic asthenia, like that of myasthenia or of Addison's disease, is to be explained by a disturbance in cholinergic and adrenergic factors, obviously the result of changes in the thymus and the adrenals which are observed with infantile amaurotic family idiocy.

R. IRVINE.

ANEURYSM OF THE CIRCLE OF WILLIS, WITH SYMPTOM-FREE INTERVAL OF TWENTY-SEVEN YEARS BETWEEN INITIAL AND FINAL RUPTURE. S. ROSEN AND W. KAUFMANN, Arch. Neurol. & Psychiat. **50:** 350 (Sept.) 1943.

Today it is well accepted that the interval of freedom from symptoms following the first attack of aneurysmal rupture may be days, months or years.

The case reported here is that of a man with an interval of twenty-seven years between the first symptoms of rupture of an aneurysm of the circle of Willis, associated with unconsciousness and xanthocromia of the cerebrospinal fluid, and the final, and fatal, episode. A survey of all the reported cases of this condition (table) reveals that twenty-two years is the longest interval of freedom from symptoms on record.

R. IRVINE.

PROGNOSIS OF MULTIPLE SCLEROSIS. H. MCINTYRE and A. MCINTYRE, Arch. Neurol. & Psychiat. **50:** 431 (Oct.) 1943.

"A clinical study of the prognosis of multiple sclerosis, based on the life charts of 55 patients, beginning with the initial episode, is presented. Three types of disseminated sclerosis are recognized: the acute, the remittent and the chronic progressive.

"The clinical course in a case of Devic's disease (neuromyelitis optica) did not appear to differ from that of the remittent type of multiple sclerosis.

"Twenty-seven patients had optic neuritis at some stage of their disease. In only 1 patient, however, were both optic nerves affected at the same time. The prognosis for the optic neuritis of multiple sclerosis is generally good; only 1 of the patients became completely blind. Optic neuritis may usher in the disease or, contrary to some opinions, may occur later in its course, years after other episodes have supervened. Seven patients showed visible swelling of the optic nerve.

"The prognosis is good for the individual attack in the remittent form of multiple sclerosis. The prognosis with respect to life is good in both the remittent and the chronic progressive form. The prognosis for life is hopeless in the acute form. Persons suffering from the remittent type may be able to lead useful lives for many years; in rare instances complete recovery occurs.

"Apoplectic episodes are not uncommon, having been experienced by 12 to 50 patients with the remittent type. The percentage probably would be higher if apopolectic episodes were sought for diligently in the history of all patients.

"No type of therapy advocated at present is of any value."

R. IRVINE.

MONOCULAR MYASTHENIA GRAVIS. S. S. WINTON, J. A. M. A. **122:** 1180 (Aug. 21) 1943.

A girl aged 17 years complained of drooping of the left upper eyelid of sudden onset. Three weeks prior to this occurrence she had suffered from moderately severe headache and a cold in the chest. Two weeks after onset of the ptosis examination revealed no other signs of myasthenia. There were no other ocular symptoms. (No record of examination of the visual acuity, visual fields or fundus was available.) Injections of prostigmine methylsulfate, 1 : 2,000, were given

twice a week. After each injection the ptosis disappeared and the eyelid regained its normal tone and power, which effect lasted only a few hours. Later 15 mg. of prostigmine bromide was given in tablet form. After several months tolerance for prostigmine developed. The best results were obtained with a combination of 15 mg. of prostigmine bromide and 0.1 Gm. of guanidine hydrochloride, given three times daily. For the past eighteen months all symptoms have remained in abeyance. A review of the literature shows that ocular abnormalities are often only the forerunners of the full-fledged disease.

The article is illustrated.

W. ZENTMAYER.

HERPES ZOSTER OPHTHALMICUS—TWO RARE MANIFESTATIONS. T. G. WYNNE PARRY and G. C. LASZLO, Brit. J. Ophth. **27:** 465 (Oct.) 1943.

A woman aged 52 suddenly became blind in the right eye. Six weeks previously she had had herpes zoster along the course of the right fifth nerve. The diagnosis was acute optic neuritis. Examination of the spinal fluid showed 44 small lymphocytes per cubic millimeter and a protein content of 30 mg. per hundred cubic centimeters. Five weeks later vision was 6/60, with an absolute scotoma. The temporal portion of the optic disk showed discoloration.

A man aged 33 had had herpes on his chest six weeks previously. Three weeks later diplopia developed as a result of paresis of the right abducens nerve. The spinal fluid showed an increased cell count, with a high protein content. The paresis cleared up.

W. ZENTMAYER.

Ocular Muscles

THE CONVERGENCE FUNCTION IN RELATION TO THE BASAL METABOLISM. S. V. ABRAHAM, Am. J. Ophth. **26:** 400 (April) 1943.

Abraham attempts to show the correlation existing between the convergence function (as studied by use of the duction method) for near vision and the general health (the basal metabolism test being used as a laboratory indicator thereof).

W. ZENTMAYER.

THE RELATIONSHIP OF ORTHOPTIC TREATMENT TO SURGERY. A. DEH. PRANGEN, Am. J. Ophth. **26:** 1298 (Dec.) 1943.

Prangen gives the following summary:

"Restoration of function seems to be the dominant purpose in the treatment of strabismus, and the connecting link between cosmetic surgery and restoration of normal function appears to be orthoptic training.

"Accurate refraction, intensive orthoptic training, and selective surgery are the means at hand for the combating of strabismus. All are of equal importance, and maximal results should be obtained through the combined use of all in proper sequence."

W. S. REESE.

TORSION IN PERSONS WITH NO KNOWN EYE DEFECT. T. G. HERMANS, Am. J. Ophth. **27:** 153 (Feb.) 1944.

Hermans concludes that torsion is a normal phenomenon of vision and that its direction is usually a disclination at the top of the vertical meridians of the eyes relative to the median plane.

W. S. REESE.

Orbit, Eyeball and Accessory Sinuses

EMPHYSEMA OF THE ORBIT: A STUDY OF SEVEN CASES. W. O. LINHART, J. A. M. A. **123:** 89 (Sept. 11) 1943.

Seven cases of emphysema of the orbit, all occurring in soldiers with a history of recent injury, are reported. In 4 cases the condition was secondary to a blow over the eye while the patient was boxing. In 3 cases the patients were struck with a shoe, a flashlight and a mushball respectively. In 5 of the cases stereoscopic roentgenograms were taken. In none could a definite fracture line be demonstrated to communicate with the nasal cavity. There were no complications in any case.

W. ZENTMAYER.

Refraction and Accommodation

EFFECTS OF ASTIGMATISM ON THE VISIBILITY OF PRINT. M. LUCKIESH and F. K. MOSS, Am. J. Ophth. **26:** 155 (Feb.) 1943.

Luckiesh and Moss observed that a —0.50 D. cylinder reduced the visibility of 12 point type from 100 to 87 per cent, and a —1.00 D. cylinder to 75 per cent, the latter representing the equivalent of loss of vision of about 4 points in type size.

W. S. REESE.

Retina and Optic Nerve

MASSIVE BILATERAL PRERETINAL TYPE OF HEMORRHAGE ASSOCIATED WITH SUBARACHNOIDAL HEMORRHAGE OF BRAIN. L. C. DREWS and J. MINCKLER, Am. J. Ophth. **27:** 1 (Jan.) 1944.

Drews and Minckler draw the following conclusions:

"1. A case of very extensive bilateral preretinal hemorrhage, associated with subarachnoidal hemorrhage from a congenital aneurysm of the communicating branch of the anterior cerebral

artery, is reported. When examined pathologically, 24 days after the onset of the brain hemorrhage, only the remains of hematoma were found in the subarachnoidal space of the optic nerves. It is concluded that hematoma had been present but was absorbed.

"2. It is suggested that if a 'preretinal' hemorrhage absorbs very rapidly the hemorrhage probably is situated beneath the internal limiting membrane where the circulation may be excellent. Such a hemorrhage really should be considered intraretinal, since the internal limiting membrane is considered a part of the retina.

"3. After one or more subarachnoidal hemorrhages, adhesions may form in the cisterna basalis on one or both sides; a later hemorrhage may then fail to produce ophthalmoscopic signs in one or both eyes.

"4. As far as I can find this case presents the largest preretinal type of hemorrhage described in the literature (about 10 disc diameters, each eye). There was no evidence that blood had been forced from the supposed hematoma of the nerve sheath through the lamina cribrosa.

"5. Why do massive preretinal hemorrhages occur in subarachnoidal hematoma of the optic-nerve sheath frequently, and rarely in ordinary papilledema?"

W. S. REESE.

Vision

VISUAL ACUITY AT LOW BRIGHTNESS-LEVELS. M. LUCKIESH and A. H. TAYLOR, Am. J. Ophth. 27: 53 (Jan.) 1944.

The authors point out that red light is more effective for a given brightness than other illuminants and that red light has many uses in wartime, in situations where concealment is vital and dark adaptation must be maintained.

W. S. REESE.

ADDITION TO DR. HAGUE'S ARTICLE

The following note from Dr. Eliott Baldwin Hague was received too late to be added to his article which appears in this issue, page 520.

"I hope that some justification for an article considerably speculative will be found in the evidence presented that it will be worth while to inject spinal fluid from patients with active cases of this syndrome into the basal cisterna of experimental animals. I shall be pleased to cooperate with those who have cases of this syndrome under their observation."

Society Transactions

EDITED BY DR. W. L. BENEDICT

COLLEGE OF PHYSICIANS OF PHILADELPHIA, SECTION ON OPHTHALMOLOGY

ALFRED COWAN, M.D., *Chairman*

WARREN S. REESE, M.D., *Secretary*

Oct. 21, 1943

Memoir of Dr. Griscom. DR. CHARLES R. HEED.

Drusen of the Optic Nerve Simulating Cerebral Tumor. DR. N. S. SCHLEZINGER (by invitation), DR. J. WALDMAN and DR. B. J. ALPERS.

This paper is published in full in this issue of the ARCHIVES, page 509.

Massive Skin Graft: Moving Picture Demonstration. DR. E. B. SPAETH.

The film illustrates some of the important factors connected with a free skin graft. The patient, with a tremendous keloid involving the entire right eye, was in an extreme state of ectropion as a result of the keloid and contraction.

A subsequent attempt to make a corneal graft proved unsuccessful because of the tremendous thickening of the cornea, accompanied by severe iridocyclitis. The skin graft was simply a matter of improving the child's cosmetic appearance.

Junius Kuhnt Macular Degeneration. DR. SAMUEL ALTMAN, Philadelphia.

This paper will be published in another journal.

DISCUSSION

DR. CHARLES E. G. SHANNON: Dr. Knox permitted me to examine this patient several weeks ago. Two features impressed me, which were pointed out by Dr. Zentmayer in the recent discussion of the case: first, the occurrence of the macular degeneration (the juvenile type) in a man of 34, and, second, the presence of the early, or hemorrhagic, stage in the right eye and the full development of the process in the left eye.

DR. WILLIAM ZENTMAYER: It is rare to be able to observe both the initial and the final stage of this condition in the same patient; so Dr. Altman's case is an instructive one.

As to the origin of the fibrous tissue, it was long held that it arose from organization of the hemorrhages. Later, Verhoeff found that the pigment epithelium of the retina was also a factor in the production of the new-formed tissue.

DR. E. B. SPAETH: The patient was referred to Wills Hospital by Dr. Andrew Knox. The photographs of the fundus were taken at Temple University by Dr. Glen Gibson. The diagnosis of the case was confirmed, on my request, by Dr. William Zentmayer.

DR. SAMUEL ALTMAN: It seems that in this disease once the damage is done and vision reaches a certain level, the condition remains stationary.

Book Reviews

Industrial Ophthalmology. By Hedwig S. Kuhn, M.D. Price, $6.50. Pp. 294, with 114 text illustrations, including 2 color plates. St. Louis: C. V. Mosby Company, 1944.

The reproach of materialism, so often brought against this so-called machine age, might be countered by citing some of its aims and achievements, idealistically inspired perhaps, yet definitely beneficial and useful. One of these is the progressive interest and activity in measures for community welfare in all its aspects, especially health, and in the active part to be taken by medicine.

While more than a little of this helpful tendency was manifest well before the flowering—if not the infancy—of industrialism, it has become at once wider and more intensive, *pari passu*, with mass production, mechanical inventions and their implications for living conditions. This has been reflected and, one might add, definitely aided by medical teaching and planning, to meet a growing demand for knowledge of the problems of social and industrial health and disease, as well as the practical details for their solution.

American ophthalmology has become aware of this situation and of the need of its cooperation in theory and practice. Although many monographs apposite to the special field of industrial ophthalmology have been published, as the author notes, here is the first comprehensive treatise on the subject.

It is authoritative, well planned and logically arranged, sound and instructive in principles and practical application and amply, as well as usefully, illustrated. Successive chapters deal with visual testing in industry (job analysis, types of teaching, tests and technic); with correction of visual defects for the job (refraction for occupation, orthoptic training, rehabilitation, economic aspects); with visual skills (types and value to management in accuracy, production and safety); visual standards and records; industrial injuries to the eyes (classification, first aid, complications); protection to the eyes; medicolegal considerations; recent advances in mechanical processes; working conditions; illumination; physical hazards to health; and the blind in industry. An appendix includes a glossary of toxic substances and their action, an ophthalmic program for industry, and a standard (approved by the American Medical Association) for the appraisal of loss of visual efficiency.

In a foreword, Dr. Albert C. Snell analyzes the visual problems confronting the industrial ophthalmologist, which include not only color vision, depth perception and special requirements of refraction, but much in the field of engineering and illumination. The same authority has contributed a chapter on "Industrial Injuries Caused by Solid Bodies," their number and cost, classification and description, as well as first aid and surgical treatment, which adds greatly to the value of this work.

The mere enumeration of these topics is evidence of the multiplicity of the problems facing social-industrial ophthalmologists, and the need for just such a work as Dr. Kuhn, an experienced worker in this field, has supplied in this well documented volume. It will be an invaluable reference handbook to all concerned with such problems.

PERCY FRIDENBERG.

Your Eyes. By Major Sidney A. Fox, Medical Corps, Army of the United States; instructor in Ophthalmology, New York University College of Medicine. Price, $2.75. Pp. 199, with 7 illustrations. New York: Alfred A. Knopf, Inc., 1944.

Preventive medicine, realizing the importance of early diagnosis for effective treatment, has been stressing a campaign of warning and information for the laity on premonitory symptoms and the essential need of professional examinations and advice. This is especially valuable in the field of ophthalmology, where apparently insignificant symptoms are ignored and ill advised self treatment, so called, is attempted only after vision has become definitely impaired. This serious situation has been dealt with by well qualified organizations, such as the National Association for the Prevention of Blindness, as well as by free lance ophthalmologists. One of these is the author of the little book under consideration, an ophthalmologist of standing and experience, who has, besides, the gift, so valuable to the popularizer in any field, of wit, a clear and illuminating style and deep interest in the needs and human nature of the lay reader.

Introductory chapters discuss in simple language how one sees, why one does not see well, sight in old age, the color world, eye glasses and the eye in traffic. Dr. Fox then turns to hygiene and first aid, ophthalmologists and optometrists and, finally, to a detailed critique of quacks and charlatans and associated rackets.

While one may question whether "the more a patient knows about himself and his ills the easier the work of the doctor becomes in preventing and curing disease," these chapters are timely and their warnings helpful.

PERCY FRIDENBERG.

Directory of Ophthalmologic Societies *

INTERNATIONAL

International Association for Prevention of Blindness

President: Dr. P. Bailliart, 66 Boulevard Saint-Michel, Paris, 6e, France.
Secretary-General: Prof. M. Van Duyse, Université de Gand, Gand, Prov. Ostflandern, Belgium.
All correspondence should be addressed to the Secretariat, 66 Boulevard Saint-Michel, Paris, 6e, France.

International Ophthalmologic Congress

President: Prof. Nordenson, Serafimerlasarettet, Stockholm, Sweden.
Secretary: Dr. Ehlers, Jerbanenegade 41, Copenhagen, Denmark.

International Organization Against Trachoma

President: Dr. A. F. MacCallan, 17 Horseferry Rd., London, England.

Pan-American Congress of Ophthalmology

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FOREIGN

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Secretary: Dr. Frederick Ridley, 12 Wimpole St., London, W. 1.

Chengtu Ophthalmological Society

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Secretary: Dr. K. S. Sun.
Place: Eye, Ear, Nose and Throat Hospital, Chengtu, China.

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Secretary: Dr. C. K. Lin, 180 Hsi-Lo-yen Chienmeng, Peiping.
Place: Peiping Union Medical College, Peiping. Time: Last Friday of each month.

German Ophthalmological Society

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All correspondence should be addressed to the Assistant Secretary.

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President: Dr. W. Niccol, 4 College Green, Gloucester, England.
Secretary: Mr. T. Harrison Butler, 61 Newhall St., Birmingham 3, England.
Place: Birmingham and Midland Eye Hospital.

North of England Ophthalmological Society

President: Dr. A. MacRae, 6 Jesmond Rd., Newcastle-upon-Tyne, England.
Secretary: Dr. Percival J. Hay, 350 Glossop Rd., Sheffield 10, England.
Place: Manchester, Bradford, Leeds, Newcastle-upon-Tyne, Liverpool and Sheffield, in rotation. Time: October to April.

Ophthalmological Society of Australia

President: Dr. A. James Flynn, 135 Macquarie St., Sydney.
Secretary: Dr. D. Williams, 193 Macquarie St., Sydney.

Ophthalmological Society of Egypt

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Secretary: Dr. Mohammed Khalil, 4 Baehler St., Cairo.
All correspondence should be addressed to the secretary, Dr. Mohammed Khalil.

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President: Mr. T. Harrison Butler, 61 Newhall St., Birmingham 3, England.
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Ophthalmology Society of Bombay

President: Dr. D. D. Sathaye, 127 Girgaum Rd., Bombay 4, India.
Secretary: Dr. H. D. Dastur, Dadar, Bombay 14, India.
Place: H. B. A. Free Ophthalmic Hospital, Parel, Bombay 12. Time: First Friday of every month.

Oxford Ophthalmological Congress

Master: Mr. P. G. Doyne, 60 Queen Anne St., London, W. 1, England.
Secretary-Treasurer: Dr. F. A. Anderson, 12 St. John's Hill, Shrewsbury, England.
Place: Oxford, England. Time: July 8-9, 1943.

Palestine Ophthalmological Society

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Secretary: Dr. E. Sinai, Tel Aviv.

Polish Ophthalmological Society

President: Dr. W. Kapuściński, 2 Waly Batorego, Poznań.
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Place: Lindley'a 4, Warsaw.

* Secretaries of societies are requested to furnish the information necessary to make this list complete and keep it up to date.

ROYAL SOCIETY OF MEDICINE, SECTION OF OPHTHALMOLOGY

President: Col. F. A. Juler, 96 Harley St., London, W. 1, England.
Secretary: Dr. Harold Ridley, 60 Queen Anne St., London, W. 1, England.

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President: Prof. Dr. Carlos Weskamp, Laprida 1159, Rosario.
Secretary: Dr. Juan M. Vila Ortiz, Córdoba 1433, Rosario.
Place: Rosario. Time: Last Saturday of every month, April to November, inclusive. All correspondence should be addressed to the President.

SOCIEDADE DE OPHTHALMOLOGIA E OTO-RHINO-LARYNGOLOGIA DA BAHIA

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Secretary: Dr. Adroaldo de Alencar, Brazil.
All correspondence should be addressed to the President.

SOCIETÀ OFTALMOLOGICA ITALIANA

President: Prof. Dott. Giuseppe Ovio, Ophthalmological Clinic, University of Rome, Rome.
Secretary: Prof. Dott. Epimaco Leonardi, Via del Gianicolo, 1, Rome.

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NATIONAL

AMERICAN MEDICAL ASSOCIATION, SCIENTIFIC ASSEMBLY, SECTION ON OPHTHALMOLOGY

Chairman: Dr. Frederick C. Cordes, 384 Post St., San Francisco.
Secretary: Dr. R. J. Masters, 23 E. Ohio St., Indianapolis.
Place: Chicago. Time: June 12-16, 1944.

AMERICAN ACADEMY OF OPHTHALMOLOGY AND OTOLARYNGOLOGY, SECTION ON OPHTHALMOLOGY

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Secretary-Treasurer: Major Brittain F. Payne, School of Aviation Medicine, Randolph Field, Texas.

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Secretary-Treasurer: Dr. L. J. Sebert, 170 St. George St., Toronto.

CANADIAN OPHTHALMOLOGICAL SOCIETY

President: Dr. R. Evatt Mathers, 34½ Morris St., Halifax, N. S.
Secretary-Treasurer: Dr. Kenneth B. Johnston, Suite 1, 1509 Sherbrooke St. W., Montreal.
Place: Halifax, N. S. Time: Aug. 4-5, 1944.

NATIONAL SOCIETY FOR THE PREVENTION OF BLINDNESS

President: Mr. Mason H. Bigelow, 1790 Broadway, New York.
Secretary: Miss Regina E. Schneider, 1790 Broadway, New York.
Executive Director: Mrs. Eleanor Brown Merrill, 1790 Broadway, New York.

SECTIONAL

ACADEMY OF MEDICINE OF NORTHERN NEW JERSEY, SECTION ON EYE, EAR, NOSE AND THROAT

President: Dr. N. Zwaifler, 46 Wilbur Ave., Newark.
Secretary: Dr. William F. Keim Jr., 25 Roseville Ave., Newark.
Place: 91 Lincoln Park South, Newark. Time: 8:45 p. m., second Monday of each month, October to May.

CENTRAL WISCONSIN SOCIETY OF OPHTHALMOLOGY AND OTOLARYNGOLOGY

President: Dr. L. J. Friend, 425 E. Grand Ave., Beloit, Wis.
Secretary: Dr. G. L. McCormick, 626 S. Central Ave., Marshfield.

NEW ENGLAND OPHTHALMOLOGICAL SOCIETY

President: Dr. Paul A. Chandler, 5 Bay State Rd., Boston.
Secretary-Treasurer: Dr. Merrill J. King, 264 Beacon St., Boston.
Place: Massachusetts Eye and Ear Infirmary, 243 Charles St., Boston. Time: 8 p. m., third Tuesday of each month from November to April, inclusive.

Pacific Coast Oto-Ophthalmological Society

President: Dr. D. H. O'Rourke, 1612 Tremont Pl., Denver.
Secretary-Treasurer: Dr. C. Allen Dickey, 450 Sutter St., San Francisco.

Puget Sound Academy of Ophthalmology and Oto-Laryngology

President: Dr. L. L. Bull, 1215–14th Ave., Seattle, Wash.
Secretary-Treasurer: Dr. Barton E. Peden, 301 Stimson Bldg., Seattle 1.
Place: Seattle or Tacoma, Wash. Time: Third Tuesday of each month except June, July and August.

Rock River Valley Eye, Ear, Nose and Throat Society

President: Dr. J. Sheldon Clark, 27 E. Stephenson St., Freeport, Ill.
Secretary-Treasurer: Dr. Harry R. Warner, 321 W. State St., Rockford, Ill.
Place: Rockford, Ill., or Janesville or Beloit, Wis. Time: Third Tuesday of each month from October to April, inclusive.

Saginaw Valley Academy of Ophthalmology and Otolaryngology

President: Dr. M. H. Pike, Midland, Mich.
Secretary-Treasurer: Dr. R. H. Criswell, 407 Phoenix Bldg., Bay City, Mich.
Place: Saginaw or Bay City, Mich. Time: Second Tuesday of each month, except July and August.

Sioux Valley Eye and Ear Academy

President: Dr. J. C. Decker, 515 Francis Bldg., Sioux City, Iowa.
Secretary-Treasurer: Dr. J. E. Dvorak, 408 Davidson Bldg., Sioux City, Iowa.

Southern Medical Association, Section on Eye, Ear, Nose and Throat

Chairman: Dr. John H. Burleson, 414 Navarro St., San Antonio, Texas.
Secretary: Dr. J. W. Jervey Jr., 101 Church St., Greenville, S. C.

Southwestern Academy of Eye, Ear, Nose and Throat

President: Dr. H. L. Brehmer, 221 W. Central Ave., Albuquerque, N. Mex.
Secretary: Dr. A. E. Cruthirds, 1011 Professional Bldg., Phoenix, Ariz.

Southwestern Michigan Triological Society

President: Dr. W. M. Dodge, 716 First National Bank Bldg., Battle Creek.
Secretary-Treasurer: Dr. Kenneth Lowe, 25 W. Michigan Ave., Battle Creek.
Time: Last Thursday of September, October, November, March, April and May.

Western Pennsylvania Eye, Ear, Nose and Throat Society

President: Dr. Ray Parker, 218 Franklin St., Johnston, Pa.
Secretary-Treasurer: Dr. J. McClure Tyson, Deposit Nat'l Bank Bldg., DuBois.

STATE

Arkansas State Medical Society, Eye, Ear, Nose and Throat Section

President: Dr. Raymond C. Cook, 701 Main St., Little Rock.
Secretary: Dr. K. W. Cosgrove, Urquhart Bldg., Little Rock.

Colorado Ophthalmological Society

President: Dr. C. A. Ringle, 912–9th Ave., Greeley.
Secretary: Dr. W. A. Ohmart, 1102 Republic Bldg., Denver.
Place: University Club, Denver. Time: 7:30 p. m., third Saturday of each month, October to May, inclusive.

Connecticut State Medical Society, Section on Eye, Ear, Nose and Throat

President: Dr. F. L. Phillips, 405 Temple St., New Haven.
Secretary-Treasurer: Dr. W. H. Turnley, 1 Atlantic St., Stamford, Conn.

Eye, Ear, Nose and Throat Club of Georgia

President: William O. Martin Jr., Doctors Bldg., Atlanta.
Secretary-Treasurer: Dr. C. K. McLaughlin, 526 Walton St., Macon.

Indiana Academy of Ophthalmology and Oto-Laryngology

President: Dr. F. McK. Ruby, Union City.
Secretary: Dr. Edwin W. Dyar Jr., 23 E. Ohio St., Indianapolis.
Place: French Lick. Time: First Wednesday in April.

Iowa Academy of Ophthalmology and Oto-Laryngology

President: Dr. J. K. Von Lackum, 117–3d St. S. E., Cedar Rapids.
Secretary-Treasurer: Dr. B. M. Merkel, 604 Locust St., Des Moines.

Louisiana-Mississippi Ophthalmological and Otolaryngological Society

President: Dr. Val H. Fuchs, 200 Carondelet St., New Orleans.
Secretary-Treasurer: Dr. Edley H. Jones, 1301 Washington St., Vicksburg, Miss.

Michigan State Medical Society, Section of Ophthalmology and Otolaryngology

Chairman: Dr. Robert H. Fraser, 25 W. Michigan Ave., Battle Creek.
Secretary: Dr. R. G. Laird, 114 Fulton St., Grand Rapids.

Minnesota Academy of Ophthalmology and Otolaryngology

President: Dr. George E. McGeary, 920 Medical Arts Bldg., Minneapolis.
Secretary: Dr. William A. Kennedy, 372 St. Peter St., St. Paul.
Time: Second Friday of each month from October to May.

Montana Academy of Oto-Ophthalmology

President: Dr. William Morrison, 208 N. Broadway, Billings, Mont.
Secretary: Dr. Fritz D. Hurd, 309 Medical Arts Bldg., Great Falls.

Nebraska Academy of Ophthalmology and Otolaryngology

President: Dr. W. Howard Morrison, 1500 Medical Arts Bldg., Omaha.
Secretary-Treasurer: Dr. John Peterson, 1307 N St., Lincoln.

New Jersey State Medical Society, Section on Ophthalmology, Otology and Rhinolaryngology

Chairman: Dr B. E. Failing, 31 Lincoln Park, Newark.
Secretary: Dr. George Meyer, 410 Haddon Ave., Camden.

New York State Medical Society, Eye, Ear, Nose and Throat Section

Chairman: Dr. Harold J. Joy, 504 State Tower Bldg., Syracuse 2.
Secretary: Dr. Maxwell D. Ryan, 660 Madison Ave., New York 21.

North Carolina Eye, Ear, Nose and Throat Society

President: Dr. Hugh C. Wolfe, 102 N. Elm St., Greensboro.
Secretary: Dr. Vanderbilt F. Couch, 104 W. 4th St., Winston-Salem.

North Dakota Academy of Ophthalmology and Oto-Laryngology

President: Dr. W. L. Diven, City National Bank Bldg., Bismarck.
Secretary-Treasurer: Dr. A. E. Spear, 20 W. Villard, Dickenson.

Oregon Academy of Ophthalmology and Oto-Laryngology

President: Dr. Paul Neely, 1020 S. W. Taylor St., Portland.
Secretary-Treasurer: Dr. Lewis Jordon, 1020 S. W. Taylor St., Portland.
Place: Good Samaritan Hospital, Portland. Time: Third Tuesday of each month.

Rhode Island Ophthalmological and Otological Society

Acting President: Dr. N. Darrell Harvey, 112 Waterman St., Providence.
Secretary-Treasurer: Dr. Linley C. Happ, 124 Waterman St., Providence.
Place: Rhode Island Medical Society Library, Providence. Time: 8:30 p. m., second Thursday in October, December, February and April.

South Carolina Society of Ophthalmology and Otolaryngology

President: Dr. J. L. Sanders, 222 N. Main St., Greenville.
Secretary: Dr. J. H. Stokes, 125 W. Cheves St., Florence.

Tennessee Academy of Ophthalmology and Otolaryngology

President: Dr. Wesley Wilkerson, 700 Church St., Nashville.
Secretary-Treasurer: Dr. W. D. Stinson, 124 Physicians and Surgeons Bldg., Memphis.

Texas Ophthalmological and Oto-Laryngological Society

President: Dr. F. H. Rosebrough, 603 Navarro St., San Antonio.
Secretary: Dr. M. K. McCullough, 1717 Pacific Ave., Dallas.

Utah Ophthalmological Society

President: Dr. R. B. Maw, 699 E. South Temple, Salt Lake City.
Secretary-Treasurer: Dr. Charles Ruggeri Jr., 1120 Boston Bldg., Salt Lake City.
Place: University Club, Salt Lake City. Time: 7:00 p. m., third Monday of each month.

Virginia Society of Oto-Laryngology and Ophthalmology

President: Dr. Mortimer H. Williams, 30½ Franklin Rd. S. W., Roanoke.
Secretary-Treasurer: Dr. Meade Edmunds, 34 Franklin St., Petersburg.

West Virginia State Medical Association, Eye, Ear, Nose and Throat Section

President: Dr. George Traugh, 309 Cleveland Ave., Fairmont.
Secretary: Dr. Welch England, 621½ Market St., Parkersburg.

LOCAL

Akron Academy of Ophthalmology and Otolaryngology

President: Dr. E. L. Mather, 39 S. Main St., Akron, Ohio.
Secretary-Treasurer: Dr. V. C. Malloy, 2d National Bank Bldg., Akron, Ohio.
Time: First Monday in January, March, May and November.

Atlanta Eye, Ear, Nose and Throat Society

President: Dr. B. M. Cline, 153 Peachtree St. N. E., Atlanta, Ga.
Acting Secretary: Dr. A. V. Hallum, 478 Peachtree St. N. E., Atlanta, Ga.
Place: Grady Hospital. Time: 6:00 p. m., fourth Monday of each month, from October to May.

Baltimore Medical Society, Section on Ophthalmology

Chairman: Dr. Ernst Bodenheimer, 1212 Eutaw Pl., Baltimore.
Secretary: Dr. Thomas R. O'Rourk, 104 W. Madison St., Baltimore.
Place: Medical and Chirurgical Faculty, 1211 Cathedral St. Time: 8:30 p. m., fourth Thursday of each month from October to March.

Birmingham Eye, Ear, Nose and Throat Club

President: Each member, in alphabetical order.
Secretary: Dr. Luther E. Wilson, 919 Woodward Bldg., Birmingham, Ala.
Place: Tutwiler Hotel. Time: 6:30 p. m., second Tuesday of each month, September to May, inclusive.

Brooklyn Ophthalmological Society

President: Dr. William B. Agan, 1 Nevins St., Brooklyn.
Secretary-Treasurer: Dr. Benjamin C. Rosenthal, 140 New York Ave., Brooklyn.
Place: Kings County Medical Society Bldg., 1313 Bedford Ave. Time: Third Thursday in February, April, May, October and December.

Buffalo Ophthalmologic Club

President: Dr. Walter F. King, 519 Delaware Ave., Buffalo.
Secretary-Treasurer: Dr. Sheldon B. Freeman, 196 Linwood Ave., Buffalo.
Time: Second Thursday of each month.

Chattanooga Society of Ophthalmology and Otolaryngology

President: Each member, in alphabetical order.
Secretary: Dr. Douglas Chamberlain, Chattanooga Bank Bldg., Chattanooga, Tenn.
Place: Mountain City Club. Time: Second Thursday of each month from September to May.

Chicago Ophthalmological Society

President: Dr. Vernon M. Leech, 55 E. Washington St., Chicago.
Secretary: Dr. W. A. Mann, 30 N. Michigan Ave., Chicago.
Place: Chicago Towers Club, 505 N. Michigan Ave. Time: Third Monday of each month from October to May.

Cincinnati General Hospital Ophthalmology Staff

Chairman: Dr. D. T. Vail, 441 Vine St., Cincinnati.
Secretary: Dr. A. A. Levin, 441 Vine St., Cincinnati.
Place: Cincinnati General Hospital. Time: 7:45 p. m., third Friday of each month except June, July and August.

Cleveland Ophthalmological Club

Chairman: Dr. Shandor Monson, 1621 Euclid Ave., Cleveland.
Secretary: Dr. Carl Ellenberger, 14805 Detroit Ave., Cleveland.
Time: Second Tuesday in October, December, February and April.

College of Physicians, Philadelphia, Section on Ophthalmology

Chairman: Dr. W. S. Reese, 1901 Walnut St., Philadelphia.
Clerk: Dr. George F. J. Kelly, 37 S. 20th St., Philadelphia.
Time: Third Thursday of every month from October to April, inclusive.

Columbus Ophthalmological and Oto-Laryngological Society

Chairman: Dr. H. D. Emswiler, 370 E. Town St., Columbus, Ohio.
Secretary-Treasurer: Dr. D. G. Sanor, 206 E. State St., Columbus, Ohio.
Place: The Neil House. Time: 6 p. m., first Monday of each month.

Corpus Christi Eye, Ear, Nose and Throat Society

Chairman: Dr. Arthur Padillo, 414 Medical Professional Bldg., Corpus Christi, Texas.
Secretary: Dr. Edgar G. Mathis, 815 Medical Arts Bldg., Corpus Christi, Texas.
Time: Second Friday of each month from October to May.

Dallas Academy of Ophthalmology and Oto-Laryngology

President: Dr. Ruby K. Daniel, Medical Arts Bldg., Dallas 1, Texas.
Secretary: Dr. Tom Barr, Medical Arts Bldg., Dallas 1, Texas.
Place: Dallas Athletic Club. Time: 6:30 p. m., first Tuesday of each month from October to June. The November, January and March meetings are devoted to clinical work.

Des Moines Academy of Ophthalmology and Otolaryngology

President: Dr. H. C. Schmitz, 604 Locust St., Des Moines, Iowa.
Secretary-Treasurer: Dr. Byron M. Merkel, 604 Locust St., Des Moines, Iowa.
Time: 7:45 p. m., third Monday of every month from September to May.

Detroit Ophthalmological Club

Chairman: Dr. Raymond S. Goux, 545 David Whitney Bldg., Detroit 26.
Secretary: Dr. Arthur Hale, 1609 Eaton Tower, Detroit.
Place: Club rooms of Wayne County Medical Society. Time: 6:30 p. m., third Thursday of each month, November through April.

Detroit Ophthalmological Society

President: Dr. Parker Heath, 1553 Woodward Ave., Detroit.
Secretary: Dr. Leland F. Carter, 1553 Woodward Ave., Detroit.
Place: Club rooms of Wayne County Medical Society. Time: Third Thursday of each month from November to April, inclusive.

Eastern New York Eye, Ear, Nose and Throat Association

President: Appointed at each meeting.
Secretary-Treasurer: Dr. Joseph L. Holohan, 330 State St., Albany.
Time: Third Wednesday in October, November, March, April, May and June.

Eastern Pennsylvania Association of Eye, Ear, Nose and Throat Physicians

President: Dr. James E. Landis, 232 N. 6th St., Reading.
Secretary-Treasurer pro tem: Dr. Paul C. Craig, 232 N. 5th St., Reading.
Time: Last week in April each year.

Fort Worth Eye, Ear, Nose and Throat Society

President: Dr. Rex Howard, 602 W. 10th St., Fort Worth, Texas.
Secretary-Treasurer: Dr. R. H. Gough, Medical Arts Bldg., Fort Worth, Texas.
Place: Medical Hall, Medical Arts Bldg. Time: 7:30 p. m., first Friday of each month except July and August.

Houston Academy of Medicine, Ophthalmological and Oto-Laryngological Section

President: Dr. Lyle J. Logue, 1304 Walker Ave., Houston, Texas.

Secretary: Dr. John T. Stough, 803 Medical Arts Bldg., Houston, Texas.

Place: Medical Arts Bldg., Harris County Medical Society Rooms. Time: 8 p. m., second Thursday of each month from September to June.

Indianapolis Ophthalmological and Oto-laryngological Society

President: Dr. Myron Harding, 23 E. Ohio St., Indianapolis.

Secretary: Dr. Kenneth L. Craft, 23 E. Ohio St., Indianapolis.

Place: Indianapolis Athletic Club. Time: 6:30 p. m., second Thursday of each month from November to May.

Kansas City Society of Ophthalmology and Oto-Laryngology

President: Dr. Edgar Johnson, 906 Grand Ave., Kansas City, Mo.

Secretary: Dr. W. E. Keith, 1103 Grand Ave., Kansas City, Mo.

Time: Third Thursday of each month from October to June. The November, January and March meetings are devoted to clinical work.

Long Beach Eye, Ear, Nose and Throat Society

Chairman: Dr. Harold Snow, 614 S. Pacific Ave., San Pedro, Calif.

Secretary-Treasurer: Dr. Oliver R. Nees, 508 Times Bldg., Long Beach, Calif.

Place: Professional Bldg. Time: Last Wednesday of each month from October to May.

Los Angeles Society of Ophthalmology and Otolaryngology

President: Dr. M. E. Trainor, 523 W. 6th St., Los Angeles.

Secretary-Treasurer: Dr. Orrie E. Ghrist, 210 N. Central Ave., Glendale, Calif.

Place: Los Angeles County Medical Association Bldg., 1925 Wilshire Blvd. Time: 6:00 p. m., fourth Monday of each month from September to May, inclusive.

Louisville Eye and Ear Society

President: Dr. Joseph S. Heitger, Heyburn Bldg., Louisville, Ky.

Secretary-Treasurer: Dr. J. W. Fish, 321 W. Broadway, Louisville, Ky.

Place: Brown Hotel. Time. 6:30 p. m., second Thursday of each month from September to May, inclusive.

Lower Anthracite Eye, Ear, Nose and Throat Society

Chairman: Each member in alphabetical order.

Secretary: Dr. James J. Monohan, 31 S. Jardin St., Shenandoah, Pa.

Medical Society of the District of Columbia, Section of Ophthalmology and Otolaryngology

Chairman: Dr. P. S. Constantinople, 1835 I St. N. W., Washington.

Secretary: Dr. Frazier Williams, 1801 I St. N. W., Washington.

Place: 1718 M St. N. W. Time: 8 p. m., third Friday of each month from October to April, inclusive.

Memphis Society of Ophthalmology and Otolaryngology

Chairman: Each member in alphabetical order.

Secretary: Dr. Sam H. Sanders, 1089 Madison Ave., Memphis, Tenn.

Place: Eye Clinic of Memphis Eye, Ear, Nose and Throat Hospital. Time: 8 p. m., second Tuesday of each month from September to May.

Milwaukee Oto-Ophthalmic Society

President: Dr. Edwin C. Bach, 324 E. Wisconsin Ave., Milwaukee.

Secretary-Treasurer: Dr. Ralph T. Rank, 238 W. Wisconsin Ave., Milwaukee.

Place: University Club. Time: 6:30 p. m., second Tuesday of each month.

Montgomery County Medical Society

Chairman: Dr. H. V. Dutrow, 1040 Fidelity Medical Bldg., Dayton, Ohio.

Secretary-Treasurer: Dr. Maitland D. Place, 981 Reibold Bldg., Dayton, Ohio.

Place: Van Cleve Hotel. Time: 6:30 p. m., first Tuesday of each month from October to June, inclusive.

Montreal Ophthalmological Society

President: Dr. J. Rosenbaum, 1396 Ste. Catherine St. W., Montreal, Canada.

Secretary: Dr. L. Tessier, 1230 St. Joseph Blvd. E., Montreal, Canada.

Time: Second Thursday of October, December, February and April.

Nashville Academy of Ophthalmology and Otolaryngology

Chairman: Dr. M. M. Cullom, 700 Church St., Nashville, Tenn.

Secretary: Dr. R. E. Sullivan, 432 Doctors Bldg., Nashvile, Tenn.

Place: St. Thomas Hospital. Time: 8 p. m., third Monday of each month from October to May

New Haven Ophthalmological Society

President: Dr. William H. Ryder, 185 Church St., New Haven, Conn.

Secretary: Dr. Frederick A. Wiess, 255 Bradley St., New Haven, Conn.

New Orleans Ophthalmological and Oto-laryngological Society

President: Dr. W. B. Clark, 1012 American Bank Bldg., New Orleans.

Secretary: Dr. Mercer G. Lynch, 1018 Maison Blanche Bldg., New Orleans.

Place: Louisiana State University Medical Bldg. Time: 8 p. m., second Tuesday of each month from October to May.

New York Academy of Medicine, Section of Ophthalmology

Chairman: Dr. Frank C. Keil, 660 Madison Ave., New York.
Secretary: Dr. Willis S. Knighton, 121 E. 61st St., New York.
Time: 8:30 p. m., third Monday of every month from October to May, inclusive.

New York Society for Clinical Ophthalmology

President: Dr. Milton Berliner, 57 W. 57th St., New York.
Secretary: Dr. Benjamin Esterman, 983 Park Ave., New York.
Place: Squibb Hall, 745–5th Ave. Time: 8 p. m., first Monday of each month from October to May, inclusive.

Oklahoma City Academy of Ophthalmology and Otolaryngology

President: Dr. James P. Luton, 117 N. Broadway, Oklahoma City.
Secretary: Dr. Harvey O. Randel, 117 N. Broadway, Oklahoma City.
Place: University Hospital. Time: Second Tuesday of each month from September to May.

Omaha and Council Bluffs Ophthalmological and Oto-Laryngological Society

President: Dr. D. D. Stonecypher, Nebraska City, Neb.
Secretary-Treasurer: Dr. W. Howard Morrison, 1500 Medical Arts Bldg., Omaha.
Place: Omaha Club, 20th and Douglas Sts., Omaha. Time: 6 p. m. dinner; 7 p. m. program; third Wednesday of each month from October to May.

Passaic-Bergen Ophthalmological Club

President: Dr. Thomas Sanfacon, 340 Park Ave., Paterson, N. J.
Secretary-Treasurer: Dr. J. Averbach, 435 Clinton Ave., Clinton, N. J.
Place: Paterson Eye and Ear Infirmary. Time: 9 p. m., last Friday of every month, except June, July and August.

Philadelphia County Medical Society, Eye Section

President: Dr. Wilfred E. Fry, 1819 Chestnut St., Philadelphia.
Secretary: Dr. Glen Gregory Gibson, 255 S. 17th St., Philadelphia.
Time: First Thursday of each month from October to May.

Pittsburgh Ophthalmological Society

President: Dr. John B. McMurray, 6 S. Main St., Washington, Pa.
Secretary: Dr. George H. Shuman, 351–5th Ave., Pittsburgh.
Place: Pittsburgh Academy of Medicine Bldg. Time: Fourth Monday of each month, except June, July, August and September.

Reading Eye, Ear, Nose and Throat Society

President: Dr. R. M. Brickbauer, Shillington, Pa.
Secretary: Dr. Paul C. Craig, 232 N. 5th St., Reading, Pa.
Place: Wyomissing Club. Time: 6:30 p. m., third Wednesday of each month from October to July.

Richmond Ophthalmological and Oto-Laryngological Society

President: Dr. Peter N. Pastore, Medical College of Virginia, Richmond, Va.
Secretary: Dr. Clifford A. Folkes, Professional Bldg., Richmond, Va.
Place: Westmoreland Club. Time: 6 p. m., second Monday of each month from October to May.

Rochester Eye, Ear, Nose and Throat Society

President: Dr. Frank Barber, 75 S. Fitzhugh St., Rochester, N. Y.
Secretary-Treasurer: Dr. Charles T. Sullivan, 277 Alexander St., Rochester, N. Y.

St. Louis Ophthalmic Society

President: Dr. C. C. Beisbarth, 3720 Washington Blvd., St. Louis.
Secretary: Dr. H. R. Hildreth, 508 N. Grand Blvd., St. Louis.
Place: Oscar Johnson Institute. Time: Clinical meeting, 5:30 p. m., dinner and scientific meeting 6:30 p. m., fourth Friday of each month from October to April, inclusive, except December.

San Antonio Ophthalmo-Oto-Laryngological Society

President: Dr. Belvin Pritchett, 705 E. Houston St., San Antonio 5, Texas.
Secretary-Treasurer: Lt. Col. John L. Matthews, AAF School of Aviation Medicine, Randolph Field, Texas.
Place: San Antonio, Brooke General Hospital, Randolph Field or San Antonio Aviation Cadet Center. Time: 7 p. m., second Tuesday of each month from October to May.

San Francisco County Medical Society, Section on Eye, Ear, Nose and Throat

Chairman: Dr. Roy H. Parkinson, 870 Market St., San Francisco.
Secretary: Dr. A. G. Rawlins, 384 Post St., San Francisco.
Place: Society's Bldg., 2180 Washington St., San Francisco. Time: Fourth Tuesday of every month except June, July and December.

Shreveport Eye, Ear, Nose and Throat Society

President: Dr. David C. Swearingen, Slattery Bldg., Shreveport, La.
Secretary-Treasurer: Dr. Kenneth Jones, Medical Arts Bldg., Shreveport, La.
Place: Shreveport Charity Hospital. Time: 7:30 p. m., first Monday of every month except July, August and September.

Spokane Academy of Ophthalmology and Oto-Laryngology

President: Dr. Clarence A. Veasey Sr., 421 W. Riverside Ave., Spokane, Wash.
Secretary: Dr. Clarence A. Veasey Jr., 421 W. Riverside Ave., Spokane, Wash.
Place: Spokane Medical Library. Time: 8 p. m., fourth Tuesday of each month except June, July and August.

Syracuse Eye, Ear, Nose and Throat Society

President: Dr. A. H. Rubenstein, 713 E. Genesee St., Syracuse, N. Y.
Secretary-Treasurer: Dr. I. H. Blaisdell, 713 E. Genesee St., Syracuse, N. Y.
Place: University Club. Time: First Tuesday of each month except June, July and August.

Toledo Eye, Ear, Nose and Throat Society

Chairman: Dr. E. W. Campbell, 316 Michigan St., Toledo, Ohio.
Secretary: Dr. L. C. Ravin, 316 Michigan St., Toledo, Ohio.
Place: Toledo Club. Time: Each month except June, July and August.

Toronto Academy of Medicine, Section of Ophthalmology

Chairman: Dr. W. R. F. Luke, 316 Medical Arts Bldg., Toronto, Canada.
Secretary: Dr. W. T. Gratton, 216 Medical Arts Bldg., Toronto, Canada.
Place: Academy of Medicine, 13 Queens Park. Time: First Monday of each month, November to April.

Washington, D. C., Ophthalmological Society

President: Dr. S. Bockoven, 1752 Massachusetts Ave., Washington, D. C.
Secretary-Treasurer: Dr. John Lloyd, 1218–16th St. N. W., Washington, D. C.
Place: Medical Society of District of Columbia Bldg., 1718 M St. N. W., Washington, D. C. Time: 7:30 p. m., first Monday in November, January, March and May.

Wilkes-Barre Ophthalmological Society

Chairman: Each member in turn.
Secretary: Dr. Samuel T. Buckman, 70 S. Franklin St., Wilkes-Barre, Pa.
Place: Office of chairman. Time: Last Tuesday of each month from October to May.

INDEX TO VOLUME 31

The asterisk (*) preceding the page number indicates an original article in the Archives. Subject entries are made for all articles. Author entries are made for original articles and society transactions. Book Reviews, Obituaries and Society Transactions are indexed under these headings in their alphabetical order under the letters B, O and S, respectively.

Abnormalities and Deformities: See under names of organs and regions
Abscess: See under names of organs and regions
Accommodation and Refraction: See also Astigmatism; Glasses; Myopia; Night Blindness; etc.
anatomic factors that influence depth of anterior chamber; their significance (errors of refraction), 106
anomalies of fusion associated with aniseikonia; preliminary report, 265
axis finder chart, *335
binocular refraction with cross cylinder technic, *34, 267
comparison of ocular imagery, 170
diagnostic value of monocular occlusion, *316
di-n-butylcarbaminoylcholine sulfate; new cycloplegic and mydriatic drug, *289
effect of undercorrection and base-in prism on myopic refractive state, 354
experimental studies on fatigue of accommodation; plan of research and observations on recession of near point of accommodation following period of interpolated work on ophthalmic ergograph, *148
fusion, projection and stereopsis, 443
ocular malingering, *223
visual phenomenon related to binocular triplopia, 353
Achromatopsia: See Color Blindness
Acid: acid-base tolerance of cornea, *279
Adenoma sebaceum; tuberous sclerosis; report of case, *68
Adler, F. H.: Juvenile macular exudative choroiditis; juvenile disciform degeneration of macula (Junius), *144
Adolescence, practical ophthalmic test which furnishes quantitative data; modification of Massachusetts vision test, *217
Adrenals, amaurosis caused by blastocytoma of, 264
hypertension with tumors of adrenal and pituitary glands, *381
Agatston, H.: Ocular malingering, *223
Air, pressure; practicability of use of contact lenses at low atmospheric pressures, *326
Albinism: See also Vitiligo
comparison of ocular reactions of pigmented and albino rabbits to normal horse serum, 559
Alkali, acid-base tolerance of cornea, *279
Allergy: See Anaphylaxis and Allergy
Alopecia, uveitis, dysacousia, poliosis and vitiligo; theory as to cause, *520, 562
Alpers, B. J.: Drusen of optic nerve simulating cerebral tumor, *509
Altitude, practicability of use of contact lenses at low atmospheric pressures, *326
Altman, S.: Junius Kuhnt macular degeneration, 563
Amaurosis: See Blindness
Amblyopia: See Blindness
American Optical Company; comparison of Ishihara and American Optical Company series of pseudoisochromatic plates, *163
Ametropia: See Accommodation and Refraction; Myopia
Amos, E. A.: Relation of ariboflavinosis and circumcorneal vascularization as observed in Navy, 263
Anaphylaxis and Allergy, comparison of ocular reactions of pigmented and albino rabbits to normal horse serum, 559
conjunctivitis and keratitis of allergic origin; analysis of 54 cases, *403
endophthalmitis phaco-anaphylactica, 350
experimental studies of ocular tuberculosis; study of increased resistance to reinoculation after recovery from ocular tuberculosis shown by immune-allergic rabbit, *413
vernal conjunctivitis, 557
Anastomosis: See Lacrimal Organs
Androgens, ocular findings in feebleminded male castrates, 559
Anesthesia, effect of local anesthetics on regeneration of corneal epithelium, *29
intravenous pentothal sodium anesthesia in ophthalmology, 259
word of caution in use of pentothal sodium in ophthalmic surgery, *134
Anesthetics: See Anesthesia
Aneurysm, arachnodactyly complicated by dislocated lens and death from rupture of dissecting aneurysm of aorta, 260
of circle of Willis, with symptom-free interval of 27 years between initial and final rupture, 560
Angioid Streaks: See Retina, blood supply
Angioma, angiomatosis retinae (von Hippel-Lindau disease); report on genealogic tree, 261
Angioscotoma: See Scotoma
Angiospasm: See Retina, blood supply
Aniseikonia: See Accommodation and Refraction
Anomalies: See under names of organs and regions
Anoxia: See Oxygen, deficiency
Aphakia: See Lens, Crystalline
Apoplexy: See Brain, hemorrhage
Apparatus: See also Instruments
experimental studies on fatigue of accommodation; plan of research and observations on recession of near point of accommodation following period of interpolated work on ophthalmic ergograph, *148
procedures and appliances that are helpful in treating industrial ocular injuries, 260
vacuum device for eyelids, *95
Aqueous Humor; aqueous veins, 107
differences of tension in chambers of eye; report of case, 175
penetration of penicillin into eye, *1
Arachnodactyly complicated by dislocated lens and death from rupture of dissecting aneurysm of aorta, 260
Marfan's syndrome, 175
Arc Flash Conjunctivitis: See Ophthalmia, electric
Ariboflavinosis: See Riboflavin
Army Medical Library, appointment to, 339
Arteries: See also Aneurysm; Arteriosclerosis; Blood pressure; Periarteritis; Thrombosis; etc.
arteritis of temporal vessels associated with loss of vision, 176
hyaloid; fibroblastic overgrowth of persistent tunica vasculosa lentis in infants born prematurely, 175
Retinal: See Retina, blood supply
temporal arteritis, 440
Arteriosclerosis, malignant renal sclerosis or malignant phase of essential hypertension, *379
Arteritis: See under Arteries
Ascher, K. W.: Corneal transplantation, 171

Astigmatism, binocular refraction with cross cylinder technic, *34, 267
effects on visibility of print, 561
great usefulness of bicylindric combinations in exploration of, 354
new approach to cross cylinder tests, 443
Atrophy: See also under names of organs and regions, as Nerves, optic; etc.
muscular; studies in diseases of muscle; progressive muscular atrophy of peroneal type associated with atrophy of optic nerves; report on family, 442
Autofundoscopy: See Retina, blood supply
Aviation and Aviators, causes of impaired vision in recently inducted soldiers, *399
comparison of Ishihara and American Optical Company series of pseudoisochromatic plates, *163
ophthalmic requirements of military services; changes from Feb. 1, 1943 to Jan. 1, 1944, *160
orthoptics in aviation, 263
practicability of use of contact lenses at low atmospheric pressures, *326
Avitaminosis: See under Vitamins; and under names of deficiency diseases

Bacilli: See Bacteria
Bacteria: See also Meningococci; Staphylococci; Typhoid; Viruses; etc.
Abortus and Melitense Group: See Undulant Fever
Calmette-Guérin: See Tuberculosis
Granulosis: See Trachoma
penicillin and sulfadiazine in treatment of experimental intraocular infections with Staphylococcus aureus and Clostridium welchii, *54
Pneumococcal: See Pneumococci
pyocyaneus; sulfadiazine iontophoresis in pyocyaneus infection of rabbit cornea, 175
subtilis; endophthalmitis due to B. subtilis following injury, 444
Tularense: See Tularemia
Typhoid Group: See Typhoid
Bahn, C. A.: Ophthalmic requirements of military services; changes from Feb. 1, 1943 to Jan. 1, 1944, *160
Baldness: See Alopecia
Bannon, R. E.: Diagnostic value of monocular occlusion, *316
Ocular occluders, 338
Beery, E. N.: Operative treatment of squint, 102
Bellows, J.: Cataract produced by anoxia, *250
Berens, C.: Experimental studies on fatigue of accommodation; plan of research and observations on recession of near point of accommodation following period of interpolated work on ophthalmic ergograph, *148
Berman locator, transscleral removal of intraocular foreign body with aid of, *207
Besnier-Boeck-Schaumann Disease: See Sarcoidosis
Best, C. H.: Ophthalmologic research in Royal Canadian Navy, 263
Bielschowsky's "lectures on motor anomalies of eyes" available, 270
Blastocytoma of adrenal gland, amaurosis caused by, 264
Blennorrhea: See Gonorrhea
Blepharitis: See Eyelids
Blepharoplasty: See under Eyelids
Blepharoptosis: See Eyelids, ptosis
Blindness: See also Vision, defective; etc.
amaurosis caused by blastocytoma of adrenal gland, 264
amaurosis following nasal hemorrhage, 260
arteritis of temporal vessels associated with loss of vision, 176
Color: See Color Blindness
Night: See Night Blindness
ocular malingering, *223
story of Red Cross Institute for Blind (1918-1925) in relation to present problem of war blinded, 177
treatment of amblyopia, 355
Blood, detection and significance of melanophore expanding substance in urine and blood with reference to retinitis pigmentosa, 111
pressure, high: changes in fundus of eye in various forms of arterial hypertension, *376
pressure, high: fundus oculi in urologic diseases associated with systemic hypertension, *427
pressure, high: hypertension associated with preeclampsia and eclampsia of pregnancy, *381
pressure, high: hypertension of renal origin, *380
pressure, high; hypertension with tumors of adrenal and pituitary glands, *381
pressure, high: malignant renal sclerosis or malignant phase of essential hypertension, *379
pressure, high; ocular changes associated with experimental renal hypertension, 116
Bloom, S.: Carl Koller, 344
Blumenfeld, L.: Rhinocanalicular anastomosis with reconstruction of lacrimal sac, *248
Boeck's Disease: See Sarcoidosis
Bones: See under names of bones
Bonser, W. H.: Causes of impaired vision in recently inducted soldiers, *399

Book Reviews:
Archivos de la Asociación para evitar la ceguera en México; L. Sánchez Bulnes, 357
Biomicroscopy of Eye: Slit Lamp Microscopy of Living Eye; M. L. Berliner, 119
Blood Transfusion in Ophthalmology, 182
Corneal Transplantation with Fresh, Preserved and Fixed Material: Experimental and Clinical Observations; O. I. Shershewskaya, 118; correction, 171
Education and Health of Partially Seeing Child; W. Hathaway, 358
Human Eye in Anatomical Transparencies; P. C. Kronfeld and others, 270
Industrial Ophthalmology; H. S. Kuhn, 564
Introduction to Clinical Perimetry; H. M. Traquair, 181
Manual of Diseases of Eye; C. H. May and C. A. Perera, 439
New Conception of Keratoconjunctivitis Sicca; H. Sjögren, 357
Strabismus: Its Etiology and Treatment; O. Wilkinson and R. W. Wilkinson, 181
Studies from School of Medicine, George Washington University for 1942-1943, 439
Trabajos publicados en 1942; H. Arruga, 269
Your Eyes; S. A. Fox, 564

Bourneville's Disease: See Sclerosis, tuberous
Bowen's Disease: See Cancer, precancer
Brain: See also Cerebellum; Meninges; Nervous System; etc.
hemorrhage; massive bilateral preretinal type of hemorrhage associated with subarachnoidal hemorrhage of brain, 561
integrated facial patterns elicited by stimulation of brain stem, 441
pathology; juvenile amaurotic idiocy; clinicopathologic study, 352
Sclerosis: See Sclerosis
temporal arteritis, 440
tumors, choked disks and low intrathecal pressure occurring in, 351
tumors; drusen of optic nerve simulating cerebral tumor, *509
tumors; multiple primary malignant neoplasm, 354
Braley, A. E.: Sulfonamide compounds in treatment of local ocular conditions, 262
Browder, J.: Problem of split macula; study of visual fields, *43
Brucellosis: See Undulant Fever
Burky, E. L.: Experimental studies of ocular tuberculosis; study of increased resistance to reinoculation after recovery from ocular tuberculosis shown by immune-allergic rabbit, *413
Burns, nonsurgical aspect of ocular injuries, 178
procedures and appliances that are helpful in treating industrial ocular injuries, 260

Campbell, C. A.: Amaurosis caused by blastocytoma of adrenal gland, 264

Cancer: See also Sarcoma; and under names of organs and regions
precancer; Bowen's disease of cornea, 176, *310
Carcinoma: See Cancer
Caruncle: See Lacrimal Organs
Case Records, importance of adequate clinical records for genetic analysis of hereditary diseases of eye, 264
Castellanos A., L.: Ariboflavinosis as probable cause of vernal conjunctivitis, *214
Castration, ocular findings in feebleminded male castrates, 559
Cataract, catgut sutures for closure of deep corneoscleral wound in operations for cataract; preliminary report, *321
changes in mineral composition of rat lenses with galactose cataract, 259
corneoscleral sutures, 262
foreign body in lens with formation of: method of extraction, 179
intracapsular extraction: statistical survey of 500 consecutive cases, *367
iridotorsion; iridectomy; cyclectomy, *242
new and improved technic for closure of cataract incisions, 109
oral use of prophylactic sulfadiazine for extractions, 350
pathologic changes in lens associated with nontraumatic iritis, *8
produced by anoxia, *250
system of intracapsular extraction: further experiences, *302
Catarrh: See Conjunctivitis, vernal; etc.
Catgut: See Sutures
Cauterization: See under names of various diseases
Cavernous Sinus, Thrombophlebitis: See Thrombosis
Cells, inclusion bodies and late fate of ganglion cells in infantile amaurotic family idiocy, 560
Cerebellum, tumor, paralysis of divergence due to, *299
Cerebrospinal Fluid, choked disks and low intrathecal pressure occurring in brain tumor, 351
experimental studies on headache, 351
Cerebrum: See Brain
Charts, axis finder chart, *335
Chemotherapy: See under names of diseases and chemotherapeutic agents, as Conjunctivitis; Eyes, diseases; Sulfonamides; Thrombosis; Trachoma; etc.
Choked Disk: See Neuritis, optic
Cholesterol: See Lipoids
Choline and Choline Derivatives, di-n-butylcarbaminoylcholine sulfate: new cycloplegic and mydriatic drug, *289
Cholinesterase at nerve termination in sphincter pupillae of turtle, 440
in amphibian sphincter pupillae, 350
Chorioretinitis: See Retinochoroiditis
Choroid, choroideremia, 354
Inflammation: See also Retinochoroiditis
inflammation: iridocyclitis and choroiditis due to "silent" sinusitis, 444
multiple primary malignant neoplasm, 354
primary sarcoma of, 354
rupture, interesting case of, 350
Choroideremia: See under Choroid
Choroiditis: See Choroid, inflammation; Retinochoroiditis
Cicatrix: See under Cornea; Eyelids
Ciliary Body: See Iridocyclitis; Uvea
Region: See Uvea
Circle of Willis: See Aneurysm
Clinics, appraisal of value of orthoptic clinic in private practice, *503
Clostridium: See Bacteria
Cogan, D. G.: Cornea; permeability characteristics of excised cornea, *408
Cohen, M.: Fundus oculi in urologic diseases associated with systemic hypertension, *427
Color Blindness, comparison of Ishihara and American Optical Company series of pseudoisochromatic plates, *463
ocular malingering, *223
Color Perception, standardized color-vision testing lantern (II), transport type, 114
Comparator: See Accommodation and Refraction
Congress: See Societies
Conjunctiva, infection of lymphoid tissue of pharynx and of conjunctiva, *331
leptotrichosis conjunctivae; further report, *423
Surgery: See Glaucoma
Conjunctivitis: See also Keratoconjunctivitis; Ophthalmia
acute gonococcal, chemotherapy in, 258
and keratitis of allergic origin; analysis of 54 cases, *403
Arc Flash: See Ophthalmia, electric
gonorrheal, penicillin in treatment; report of case, *162
Granular: See Trachoma
leptotrichosis conjunctivae; further report, *423
meningococcic, *245, *284
Pannus: See Trachoma
Parinaud's oculoglandular syndrome, 258
sulfonamide compounds in treatment of local ocular conditions, 262
vernal, 557
vernal, ariboflavinosis as probable cause of, *214
Contact Glasses: See Glasses
Contusions: See Eyes, injuries
Convergence: See Strabismus
Converse, J. M.: Two plastic operations for repair of orbit following severe trauma and extensive comminuted fracture, *323
Convulsions: See Epilepsy
Cordes, F. C.: Dickey operation for ptosis; results in 21 patients and 30 lids, *461
Sanford Robinson Gifford, 340
Cornea, acid-base tolerance of, *279
Bowen's disease of, 176, *310
catgut sutures for closure of deep corneoscleral wound in operations for cataract; preliminary report, *321
congenital opacities of, *138
development of anterior peripheral synechiae in experimental acute glaucoma, *481
effect of local anesthetics on regeneration of corneal epithelium, *29
epithelial tumors of limbus, 112
Fistula: See under Fistula
fungous diseases of; report of cases, 176
Groenouw's dystrophy, 259
Inflammation: See Keratitis
management of lacerations, 180
new aid in removal of foreign bodies; topical application of silver nitrate, *129
nodular keratitis, 106
Pannus: See Trachoma
permeability characteristics of excised cornea, *408
production and treatment of experimental pneumococcal hypopyon ulcers in rabbit, 355
relation of ariboflavinosis and circumcorneal vascularization as observed in Navy, 263
sulfadiazine iontophoresis in pyocyaneus infection of rabbit cornea, 175
Surgery: See Cataract; Glaucoma
transplantation, 171
treatment of herpetic and dendritic ulcers, 176
vascularization problems, 258
white rings (Coats), 106
Correction in transcript of article by Dr. H. Saul Sugar entitled "Guides in the Operative (Cosmetic) Treatment of Nonaccommodative Concomitant Squint in Adults" (Arch. Ophth. 30: 593 [Nov.] 1943), 117
Craniopharyngioma, problem of split macula; study of visual fields, *43
Cranium, pressure; experimental studies on headache, 351
Crystalline Lens: See Lens, Crystalline
Curare, myasthenia gravis; curare sensitivity; new diagnostic test and approach to causation, 352
Cushing's Disease: See Pituitary Body
Cutter, I. S.: Sanford Robinson Gifford, 340
Cyclectomy: See Cataract
Cyclitis: See Iridocyclitis
Cyclodiathermy: See Glaucoma
Cycloplegia: See Accommodation and Refraction
Cysts: See under names of organs and regions, as Nerves, optic; etc.

Dacryocystorhinostomy: See Lacrimal Organs
Daniel, R. K.: Healing of iris in rabbits following experimental iridectomy, *292
Dark Adaptation: See Accommodation and Refraction
Davis, F. A.: Catgut sutures for closure of deep corneoscleral wound in operations for cataract; preliminary report, *321
Intracapsular cataract extraction: statistical survey of 500 consecutive cases, *367
Davis, W. T., appointment to Army Medical Library, 339
Day, A. A.: Leptotrichosis conjunctivae: further report, *423
Deafness: uveitis, dysacousia, alopecia, poliosis and vitiligo; theory as to cause, *520, 562
Deformities: See under names of organs and regions
Degeneration: See Macula Lutea
Denig, R.: Iridotorsion; iridectomy; cyclectomy, *242
Prolapse of uvea; treatment and significance in interpretation of sympathetic ophthalmia and glaucoma, *232
Depth Perception: See Space, perception
Descemet Membrane: See Cornea
Detergents, penetration of penicillin into eye, *1
Diabetes Mellitus, diabetic retinitis, 111, 112
diabetic retinopathy, *96
Diathermy: See under names of diseases, organs and regions
Dickey Operation: See Eyelids, ptosis
Dienst, E. C.: Pathologic changes in eye associated with subacute bacterial endocarditis; report of 5 cases with autopsy, *198
Di Grandi, J.: Penetration of penicillin into eye, *1
Dimitry, T. J.: Socket after enucleation and artificial eye, *18
Di-n-butylcarbaminoylcholine sulfate: new cycloplegic and mydriatic drug, *289
Diplegia: See Paralysis
Directory of ophthalmologic societies, 121, 183, 271, 359, 445, 565
Disk, Optic: See Nerves, optic
Drusen: See Nerves, optic
Dysacousia: See Deafness
Dystrophy: See under Cornea; etc.

Eagan, E. F.: Iritis, retinal hemorrhage and changes in lens following injection of typhus vaccine; report of case, *336
Ear: See Deafness
Echlin, F. A.: Tuberous sclerosis; report of case, *68
Eclampsia, hypertension associated with preeclampsia and eclampsia of pregnancy, *381
Edelson, D.: Staphylococcic thrombophlebitis of cavernous sinus; report of case, with recovery with chemotherapy and heparin, *329
Edema: See Macula Lutea
Education, postgraduate course in neuromuscular anomalies of eyes, 339
Elkonometer: See Accommodation and Refraction
Electrocoagulation: See under specific headings
Electrosurgery: See under specific headings
Ellett, E. C.: Appraisal of value of orthoptic clinic in private practice, *503
Ellis, V. M.: Operative treatment of paralysis of external rectus muscle, *254
Elwyn, H.: Changes in fundus of eye in various forms of arterial hypertension, *376
Embolism: See Thrombosis
Emergency room service at Wills Hospital, *211
Emphysema of orbit; study of 7 cases, 561
Endocarditis, pathologic changes in eye associated with subacute bacterial endocarditis; report of 5 cases with autopsy, *198
Endophthalmitis: See Eyes, diseases
Entropion: See Eyelids
Enucleation: See Cataract; Eyes, surgery; Glaucoma; etc.
Epilepsy, retinal arterial tension associated with epilepsy, 264
Epithelium: See Cornea; Lens, Crystalline
Ergograph, experimental studies on fatigue of accommodation; plan of research and observations on recession of near point of accommodation following period of interpolated work on ophthalmic ergograph, *148
Esophoria: See Strabismus
Evans, J. N.: Modifications of tonometer, *334
Problem of split macula; study of visual fields, *43
Evisceration: See Eyes, surgery
Ewing Operation: See Eyelids
Exophoria, ocular findings in feebleminded male castrates, 560
Exophthalmos, monocular, due to hyperthyroidism in patient with Duane syndrome, 116; correction, 338
Extremities, blood supply; evaluation of ocular angiospasm, *453
Eyelids, autoinoculation of eyelids with vaccinia, *539
colored moving pictures of plastic surgical procedures on eye, 264
modified Ewing operation for cicatricial entropion, 178
ptosis, combined operation, 178
ptosis, Dickey operation for; results in 21 patients and 30 lids, *461
ptosis; monocular myasthenia gravis, 560
sulfonamide compounds in treatment of local ocular conditions (blepharitis), 262
vacuum device for, *95
Eyes: See also Orbit; Vision; and under names of special structures and diseases
Abnormalities: See under names of special structure of eye
Accommodation and Refraction: See Accommodation and Refraction
anatomic factors that influence depth of anterior chamber; their significance (errors of refraction), 106
Anesthesia: See Anesthesia
Anomalies: See under names of special structures of eye and diseases
artificial; restoration of lower cul-de-sac, 353
Bielschowsky's "lectures on motor anomalies of eyes" available, 270
Blood Supply: See also Retina, blood supply
blood supply; clinical vascular physiology of eye, 443
changes in amaurotic family idiocy (infantile type of Tay-Sachs disease); histopathologic observations in case, 441
comparison of ocular reactions of pigmented and albino rabbits to normal horse serum, 559
Cysts: See under names of special structures of eye
diagnostic value of monocular occlusion, *316
Diseases: See also Iridocyclitis; Glaucoma; Ophthalmia; Trachoma; etc.
diseases; chemotherapy in ophthalmology, 437
diseases; endophthalmitis due to B. subtilis following injury, 444
diseases; endophthalmitis phaco-anaphylactica, 350
diseases; fever therapy in ophthalmology, 436
diseases; general and local administration of penicillin, 114
diseases; geographical distribution of ocular infections, 559
diseases; importance of adequate clinical records for genetic analysis of hereditary diseases of eye, 264
diseases; psychoneurotic factor in ophthalmic practice, 351
diseases; sulfonamide compounds in treatment of local ocular conditions, 262
diseases; vitamins in ophthalmology, 259
Examination: See also Accommodation and Refraction; Foreign Bodies; Vision, tests; etc.
examination; present limits of gonioscopy, 351
Foreign Bodies in: See Foreign Bodies
Gonorrhea: See Gonorrhea

Eyes—Continued
Injuries: See also under Cataract; Foreign Bodies
injuries; "arc flash" conjunctivitis; actinic conjunctivitis from electric welding arc, 107
injuries; changes in ciliary body after contusio bulbi in which only anterior segment of eye is affected, 107
injuries; eye surgery in wartime, 177
injuries, industrial and domestic, 438
injuries; Lagrange's law of indirect ocular war injuries, 177
injuries; measuring eye flash from arc welding, 260
injuries, nonpenetrating, 559
injuries, nonsurgical aspect of, 178
injuries; procedures and appliances that are helpful in treating industrial ocular injuries, 260
injuries; traumatic edema of macula, 108
injuries; treatment of photophthalmia following exposure to rays of welding arc, 108
manifestations of head injuries, 434
massive skin graft; moving picture demonstration, 563
Movements: See also Paralysis; Strabismus; etc.
movements; convergence function in relation to basal metabolism, 561
movements; near horizontal phoria and duction tests, 353
Muscles: See also Paralysis; Phorias; Strabismus
muscles; observations and experimental studies on physiology of ciliary muscle, 109
ocular changes associated with experimental renal hypertension, 116
ocular findings in case of periarteritis nodosa, 176
ocular findings in feebleminded male castrates, 559
ocular malingering, *223
ocular occluders, 170, 338
ophthalmic ointments, 353
ophthalmic requirements of military services; changes from Feb. 1, 1943 to Jan. 1, 1944, *160
Paralysis: See Paralysis
parasites; ophthalmoscopic observations of microfilarias in vitreous of patients infected with onchocerciasis, 353
pathologic changes associated with subacute bacterial endocarditis; report of 5 cases with autopsy, *198
penetration of penicillin into eye, *1
penicillin and gramicidin as ocular chemotherapeutic agents, *165
penicillin and sulfadiazine in treatment of experimental intraocular infections with Staphylococcus aureus and Clostridium welchii, *54
physiology; gonioscopic study on canal of Schlemm, 109
Pigmentation: See Retinitis pigmentosa; and under special structures of eyes
postgraduate course in neuromuscular anomalies of, 339
Refraction: See Accommodation and Refraction
role of iron, copper, zinc and manganese in metabolism of ocular tissues with reference to lens, 258
Sarcoma: See Sarcoma
study of mustard-gas lesions of eye of rabbits and men, 559
Surgery: See also Cataract; Cornea; Glaucoma; etc.
surgery; intravenous pentothal sodium anesthesia in ophthalmology, 259
surgery; socket after enucleation and artificial eye, *18
surgery; technic of enucleation with implantation of prothesis, 263
surgery; word of caution in use of pentothal sodium in ophthalmic surgery, *134
Tension: See Glaucoma; Tension
Tuberculosis: See Tuberculosis
tumors; retroillumination, 351
tumors; x-ray therapy of inflammatory and neoplastic diseases of eyes, 444

Face, Lagrange's law of indirect ocular war injuries, 177
Falls, H. F.: Word of caution in use of pentothal sodium in ophthalmic surgery, *134
Fatigue, experimental studies on fatigue of accommodation; plan of research and observations on recession of near point of accommodation following period of interpolated work on ophthalmic ergograph, *148
Feebleмindedness: See also Idiocy
ocular findings in feebleminded male castrates, 559
Fever: See Typhoid; Undulant Fever; etc.
Therapy: See Eyes, diseases
Fibrosarcoma, recurrence in orbit 7 years after removal; results of roentgen irradiation, 265
Field, H. B.: Comparison of ocular imagery, 170
Fingers and Toes, Abnormalities: See Arachnodactyly
Fistula of cornea; method of treatment, 107
Focal Infection: See Infection, focal
Foramen Hyaloidaea: See Vitreous Humor
Foreign Bodies, case of removal of nonmagnetic foreign body from ciliary region, 441
detachment of retina resulting from traction exerted by intraocular foreign body, 179
in lens with formation of cataract; method of extraction, 179
intraocular, 434
intraocular, in peacetime and in wartime and problem of their removal, 260
location in eye with contact lens, 180
new aid in removal of foreign bodies of cornea; topical application of silver nitrate, *129
transscleral removal of intraocular foreign body with aid of Berman locator, *207
Fovea Centralis: See Macula Lutea
Franklin, Benjamin, bifocal glasses, 102
Frey, W. G.: Monocular exophthalmos due to hyperthyroidism in patient with Duane syndrome, 116; correction, 338
Friedenwald, H.: Carl Hamburger, 557
Friedenwald, J. S.: Acid-base tolerance of cornea, *279
Fritschi, U.: Dickey operation for ptosis; results in 21 patients and 30 lids, *461
Fundus Oculi: See under Retina

Galactose, changes in mineral composition of rat lenses with galactose cataract, 259
Gallagher, J. R.: Practical ophthalmic test which furnishes quantitative data; modification of Massachusetts vision test, *217
Ganglion: See Nervous System; Neurons
Gartner, S.: Pathologic changes in eye associated with subacute bacterial endocarditis; report of 5 cases with autopsy, *198
Gas, poisoning; study of mustard-gas lesions of eyes of rabbits and men, 559
Genetics: See Heredity
Geography, geographical distribution of ocular infections, 559
Gifford, S. R.: Evaluation of ocular angiospasm, *453
Leptotrichosis conjunctivae; further report, *423
Gilhooly, J. P.: Colored moving pictures of plastic surgical procedures on eye, 264
Gillette, D. F.: New aid in removal of foreign bodies of cornea; topical application of silver nitrate, *129
Glasses: See also Accommodation and Refraction
Benjamin Franklin bifocal glasses, 102
binocular refraction with cross cylinder technic, *34, 267
effect of undercorrection and base-in prism on myopic refractive state, 354
location of foreign body in eye with contact lens, 180
ocular occluders, 170, 338
practicability of use of contact lenses at low atmospheric pressures, *326
Glaucoma: See also Tension
anatomic factors that influence depth of anterior chamber; their significance (errors of refraction), 106
aqueous veins, 107
associated with nevus flammeus; report of case in which cyclodiathermy was used in attempt to control intraocular pressure, 440

Glaucoma—Continued
development of anterior peripheral synechiae in experimental acute glaucoma, *481
effect of mydriatrics on intraocular pressure in so-called primary wide-angle glaucoma, 177
evaluation of operations, 176
gonioscopic study on canal of Schlemm, 109
lens extractions following filtering operation for, 350
nervous factor in origin of simple glaucoma, *384
present limits of gonioscopy, 351
prolapse of uvea; treatment and significance in interpretation of sympathetic ophthalmia and glaucoma, *232
pupillary reactions of seemingly unaffected eye in clinically unilateral simple glaucoma; pupillographic contributions to diagnosis of glaucoma in preclinical stage, *392
Glioblastoma, multiple primary malignant neoplasm, 354
Gonioscopy: See Eyes, examination; Eyes, physiology; Glaucoma
Gonorrhea, penicillin in treatment of gonorrheal conjunctivitis; report of case, *162
Gordon, B. L.: Ocular tuberculosis; its relation to general tuberculosis, *541
Graef, I.: Ocular changes associated with experimental renal hypertension, 116
Gramicidin and penicillin as ocular chemotherapeutic agents, *165
Granuloma, Malignant: See Hodgkin's Disease
Griffey, W. P.: Penicillin in treatment of gonorrheal conjunctivitis; report of case, *162
Grönblad-Strandberg Syndrome: See Pseudoxanthoma elasticum; Retina, blood supply
Gumma: See under names of organs and regions
Gundersen, T.: Effect of local anesthetics on regeneration of corneal epithelium, *29
Guyton, J. S.: Role of sarcoidosis and of brucellosis in uveitis, *469

Hague, E. B.: Uveitis, dysacousia, alopecia, poliosis and vitiligo; theory as to cause, *520, 562
Hair, color of; uveitis, dysacousia, alopecia, poliosis and vitiligo; theory as to cause, *520, 562
Diseases: See Alopecia
Halpern, H. J.: Iritis, retinal hemorrhage and changes in lens following injection of typhus vaccine; report of case, *336
Harned, J. W.: Pseudoaphakia fibrosa; report of case, *253
Harris, R. H.: Comparison of Ishihara and American Optical Company series of pseudoisochromatic plates, *163
Head: See also Cranium
injuries, eye manifestations of, 434
Headache, experimental studies on, 351
Hemeralopia: See Night Blindness
Hemianopsia, bilateral thrombosis of posterior calcarine arteries with sparing of macular vision, 352
Hemorrhage: See Brain; Meninges; Nose; Retina; etc.
Heparin: See Thrombosis
Heredity, importance of adequate clinical records for genetic analysis of hereditary diseases of eye, 264
Herpes, treatment of herpetic and dendritic ulcers, 176
zoster ophthalmicus; 2 rare manifestations, 561
Herrmann, H.: Acid-base tolerance of cornea, *279
Heterochromia: See Iris, pigmentation
von Hippel's Disease: See Angioma; Retina
Hirsch, E. O.: Cornea; permeability characteristics of excised cornea, *408
Hodgkin's Disease associated with uveitis; report of case, *517
Hormones: See Androgens; etc.
Hospitals, emergency room service at Wills Hospital, *211
Hughes, W. F., Jr.: Acid-base tolerance of cornea, *279
Hyaloid Canal: See under Vitreous Humor
Hydrogen Ion Concentration, acid-base tolerance of cornea, *279
Hydronephrosis, fundus oculi in urologic diseases associated with systemic hypertension, *427
Hyperergy: See Anaphylaxis and Allergy
Hypertension: See Blood pressure, high
Ocular: See Tension
Hyperthyroidism: See Thyroid
Hypertonia: See Tension
Hypophysis: See Pituitary Body
Hypopyon: See under Cornea
Hypotony: See Tension

Idiocy: See also Feeblemindedness
changes in eyes in amaurotic family idiocy (infantile type of Tay-Sachs disease); histopathologic observations in case, 441
inclusion bodies and late fate of ganglion cells in infantile amaurotic family idiocy, 560
juvenile amaurotic; clinicopathologic study, 352
Illumination: See Lighting
Imbecility: See Idiocy
Immunity: See also Anaphylaxis and Allergy; etc.
experimental studies of ocular tuberculosis; study of increased resistance to reinoculation after recovery from ocular tuberculosis shown by immune-allergic rabbit, *413
Industrial Diseases, "arc flash" conjunctivitis; actinic conjunctivitis from electric welding arc, 107
distribution of epidemic keratoconjunctivitis in United States, 435
Industrial and domestic injuries of eye, 438
injury to ciliary body without iridocyclitis, 179
measuring eye flash from arc welding, 260
procedures and appliances that are helpful in treating industrial ocular injuries, 260
significance of visual defects in war production effort, 435
treatment of photophthalmia following exposure to rays of welding arc, 108
Infants, Premature: See Premature Infants
Infection: See also Immunity
focal, 259
Inflammation, Corneal: See Keratitis
Ocular: See under special structures of eyes
Injuries: See Trauma; and under names of organs and regions, as Cornea; Eyes; Face; Head; etc.
Instruments: See also Apparatus
appraisal of value of orthoptic clinic in private practice, *503
comparison of ocular imagery, 170
modification of Arruga's speculum, 109
modifications of tonometer, *334
orthoptic, evaluation of, 350
transscleral removal of intraocular foreign body with aid of Berman locator, *207
Insulin: See Diabetes Mellitus
Intraocular Tension: See Tension
Iontophoresis: See under Cornea
Iridectomy: See Cataract; Iris
Iridocyclitis: See also Ophthalmia, sympathetic
and choroiditis due to "silent" sinusitis, 444
purulent, intraocular injection of sulfanilamide in case of, 444
Iridotorsion: See Cataract
Iris: See also Pupils
development of anterior peripheral synechiae in experimental acute glaucoma, *481
healing in rabbits following experimental iridectomy, *292
Inflammation: See also Iridocyclitis
inflammation; iritis, retinal hemorrhage and changes in lens following injection of typhus vaccine; report of case, *336
inflammation; pathologic changes in lens associated with nontraumatic iritis, *8
pigmentation; unilateral melanosis irides, 106
Iritis: See Iris, inflammation
Ishihara Test: See Color Blindness

Jaeckle, C. E.: Practicability of use of contact lenses at low atmospheric pressures, *326
Jensen's Disease: See Retinochoroiditis
Johnson, R. M.: Causes of impaired vision in recently inducted soldiers, *399

Kamellin, S.: Uveitis associated with Hodgkin's disease; report of case, *517
Keloid, massive skin graft; moving picture demonstration, 564
Keratitis: See also Keratoconjunctivitis
and conjunctivitis of allergic origin; analysis of 54 cases, *403
occurring with molluscum contagiosum, *64
Trachomatous: See Trachoma
Keratoconjunctivitis, epidemic, distribution in United States, 435
epidemic, from subjective viewpoint, 559
virus isolated from pemphigus-like keratoconjunctivitis, 258
Keratoplasty: See under Cornea
Kidneys, hypertension of renal origin, *380
malignant renal sclerosis or malignant phase of essential hypertension, *379
ocular changes associated with experimental renal hypertension, 116
polycystic; fundus oculi in urologic diseases associated with systemic hypertension, *427
Kinsey, V. E.: Cornea; permeability characteristics of excised cornea, *408
Kirby, D. B.: Further experiences with system of intracapsular extraction of cataract, *302
Klunzinger, W. R.: Autoinoculation of eyelids with vaccinia, *539
Knapp, A.: Adolph O. Pflngst, 347
Charles Edward Finlay, 346
Edmond Eduard Blaauw, 349
George Lindsay Johnson, 256
Rayner Derry Batten, 257
Sanford Robinson Gifford, 340
Knauber, E.: Anomalies of fusion associated with aniseikonia; preliminary report, 265
Kornzweig, A. L.: Recurrence of fibrosarcoma of orbit 7 years after removal; results of roentgen irradiation, 265
Kost, P. F.: Meningococcic conjunctivitis, *245
Koyanagi-Vogt Syndrome: See under Uvea, inflammation
Krönlein Operation: See Nerves, optic
Krug, E. F.: Tuberous sclerosis; report of case, *68

Lacrimal Canal: See Lacrimal Organs
Lacrimal Organs, dacryocystorhinostomy: logical treatment for occlusion of lacrimal sac, 350
primary tumors of, 263
rhinocanalicular anastomosis, *432
rhinocanalicular anastomosis with reconstruction of lacrimal sac, *248
Lagrange's Law: See Eyes, injuries
Lambert, R. K.: Ocular changes associated with experimental renal hypertension, 116
Lamina Sclerae: See Sclera
Vitrea: See Choroid
Lancaster, W. B.: Comparison of ocular imagery, 170
Langdon, H. M.: Operative treatment of paralysis of external rectus muscle, *254
Lebensohn, J. E.: Binocular refraction with cross cylinder technic, 268
Lectures, Bielschowsky's "lectures on motor anomalies of eyes" available, 270
Lee, O. S., Jr.: Keratitis occurring with molluscum contagiosum, *64
Lehrfeld, L.: Vernal conjunctivitis, 557
Lemere, H. B.: Vacuum device for eyelids, *95
Lens, Crystalline; arachnodactyly complicated by dislocated lens and death from rupture of dissecting aneurysm of aorta, 260
arachnodactyly (Marfan's syndrome), 175
changes in mineral composition of rat lenses with galactose cataract, 259
endophthalmitis phaco-anaphylactica, 350
Lens, Crystalline—Continued
fibroblastic overgrowth of persistent tunica vasculosa lentis in infants born prematurely, 175
foreign body in lens with formation of cataract; method of extraction, 179
iritis, retinal hemorrhage and changes in lens following injection of typhus vaccine; report of case, *336
Opacity: See Cataract
pathologic changes in lens associated with nontraumatic iritis, *8
pseudoaphakia fibrosa; report of case, *253
role of iron, copper, zinc and manganese in metabolism of ocular tissues with reference to lens, 258
Leopold, I. H.: Diabetic retinopathy, *96
Leptotrichosis conjunctivae; further report, *423
Levine, A. S.: Pupillographic studies; periodic sympathetic spasm and relaxation and role of sympathetic nervous system in pupillary innervation, *74
Liebman, S. D.: Effect of local anesthetics on regeneration of corneal epithelium, *29
Light, "arc flash" conjunctivitis; actinic conjunctivitis from electric welding arc, 107
measuring eye flash from arc welding, 260
treatment of photophthalmia following exposure to rays of welding arc, 108
Lighting, ophthalmologic research in Royal Canadian Navy, 263
visual acuity at low brightness-levels, 562
Limbus Conjunctivae: See under Conjunctiva
Corneae: See Cornea
Lindau's Disease: See under Retina
Linhart, W. O.: Conjunctivitis and keratitis of allergic origin; analysis of 54 cases, *403
Lipoids, traumatic liporrhagia retinalis (Verhoeff); Purtscher's disease, *191
Lippmann, O.: Paralysis of divergence due to cerebellar tumor, *299
Lowenstein, O.: Nervous factor in origin of simple glaucoma, *384
Pupillary reactions of seemingly unaffected eye in clinically unilateral simple glaucoma; pupillographic contributions to diagnosis of glaucoma in preclinical stage, *392
Pupillographic studies; periodic sympathetic spasm and relaxation and role of sympathetic nervous system in pupillary innervation, *74
Lymphogranuloma, Hodgkin's: See Hodgkin's Disease
Lymphoid Tissue, infection of lymphoid tissue of pharynx and of conjunctiva, *331

McCulloch, R. J. P.: Corneoscleral sutures, 262
Macklin, M. T.: Importance of adequate clinical records for genetic analysis of hereditary diseases of eye, 264
MacMillan, J. A.: Primary tumors of lacrimal gland, 263
Macula Lutea: See also Vision
Junius Kuhnt macular degeneration, 563
juvenile macular exudative choroiditis; juvenile disciform degeneration of macula (Junius), *144
problem of split macula; study of visual fields, *43
traumatic edema of, 108
Malingering, ocular, *223
Malta Fever: See Undulant Fever
Mangiaracine, A. B.: Meningococcic conjunctivitis, *284
Marfan's Syndrome: See Arachnodactyly
Masor, P. L.: Axis finder chart, *335
Massachusetts vision test, practical ophthalmic test which furnishes quantitative data; modification of, *217
Medicine: See Ophthalmology: etc.
Military: See Military Medicine
Meibomian Glands: See Eyelids
Melanin, pigmentation; detection and significance of melanophore expanding substance in urine and blood with reference to retinitis pigmentosa, 111

Melanoma, multiple primary malignant neoplasm, 354
Melanophore: See Melanin, pigmentation
Meninges, massive bilateral preretinal type of hemorrhage associated with subarachnoidal hemorrhage of brain, 561
Meningococci, meningococcic conjunctivitis, *245, *284
Metabolism, convergence function in relation to basal metabolism, 561
Meyer, K.: Penetration of penicillin into eye, *1
Microfilarias: See Onchocerciasis
Miles, N. E.: Causes of impaired vision in recently inducted soldiers, *399
Military Medicine: See also Aviation and Aviators; Gas, poisoning; Naval Medicine; Recruits; etc.
eye surgery in wartime, 177
intraocular foreign bodies in peacetime and in wartime and problem of their removal, 260
Lagrange's law of indirect ocular war injuries, 177
nonsurgical aspect of ocular injuries, 178
ocular malingering, *223
ophthalmic requirements of military services; changes from Feb. 1, 1943 to Jan. 1, 1944, *160
story of Red Cross Institute for Blind (1918-1925) in relation to present problem of war blinded, 177
two plastic operations for repair of orbit following severe trauma and extensive comminuted fracture, *323
Minerals, role of iron, copper, zinc and manganese in metabolism of ocular tissues with reference to lens, 258
Minsky, H.: Transscleral removal of intraocular foreign body with aid of Berman locator, *207
Miosis: See Pupils
Molluscum Contagiosum, keratitis occurring with, *64
Moving Pictures, colored, of plastic surgical procedures on eye, 264
Mulberger, R. D.: Operative treatment of paralysis of external rectus muscle, *254
Muscles, choline esterase at nerve termination in sphincter pupillae of turtle, 440
Ciliary: See Eyes, muscles
facial; integrated facial patterns elicited by stimulation of brain stem, 441
Ocular: See Eyes, muscles; Strabismus
studies in diseases of; progressive muscular atrophy of peroneal type associated with atrophy of optic nerves; report on family, 442
Mustard Gas: See Gas, poisoning
Myasthenia Gravis; curare sensitivity; new diagnostic test and approach to causation, 352
monocular, 560
Mycosis, fungous diseases of cornea; report of cases, 176
Mydriatics: See Pupils
Myelitis; prognosis of multiple sclerosis, 561
Myopia, 110
convergence function in relation to basal metabolism, 561
effect of undercorrection and base-in prism on myopic refractive state, 354
high congenital, with convergent strabismus, 443

Narcosis: See Anesthesia
Nasolacrimal Duct: See Lacrimal Organs
Naval Medicine: See also Aviation and Aviators; Military Medicine; Recruits; etc.
ophthalmic requirements of military services; changes from Feb. 1, 1943 to Jan. 1, 1944, *160
ophthalmologic research in Royal Canadian Navy, 263
relation of ariboflavinosis and circumcorneal vascularization as observed in Navy, 263
Navies: See Naval Medicine
Nearsightedness: See Myopia
Nelson, D.: Cataract produced by anoxia, *250
Nerves: See also Nervous System; Neuritis; Paralysis; etc.
Cells: See Neurons
choline esterase at nerve termination in sphincter pupillae of turtle, 440
optic; drusen of optic nerve simulating cerebral tumor, *509
optic, Krönlein operation for case of cyst, 113
Nerves—Continued
optic; pathologic changes in eye associated with subacute bacterial endocarditis; report of 5 cases with autopsy, *198
optic; studies in diseases of muscle; progressive muscular atrophy of peroneal type associated with atrophy of optic nerves; report on family, 442
optic: use of pseudoisochromatic charts in detecting central scotomas due to lesions in conducting pathways, 351
Paralysis: See under Paralysis
Nervous System: See also Brain; Cerebellum; Nerves; Neurons; Reflex; etc.
nervous factor in origin of simple glaucoma, *384
pupillary reactions of seemingly unaffected eye in clinically unilateral simple glaucoma; pupillographic contributions to diagnosis of glaucoma in preclinical stage, *392
pupillographic studies; periodic sympathetic spasm and relaxation and role of sympathetic nervous system in pupillary innervation, *74
Neuritis, optic; choked disks and low intrathecal pressure occurring in brain tumor, 351
optic; prognosis of multiple sclerosis, 560
Neurocytoma; amaurosis caused by blastocytoma of adrenal gland, 264
Neurons, inclusion bodies and late fate of ganglion cells in infantile amaurotic family idiocy, 560
Neuroses and Psychoneuroses, psychoneurotic factor in ophthalmic practice, 351
Nevi: See also Angioma
flammeus associated with glaucoma; report of case in which cyclodiathermy was used in attempt to control intraocular pressure, 440
Nicholls, J. V. V.: Orthoptics in aviation, 263
Night Blindness, improvement with vitamin D, including experimental production of retinitis pigmentosa and its treatment in humans with vitamin D, 113
Night Vision: See Accommodation and Refraction
Nose, hemorrhage, amaurosis following, 260
rhinocanalicular anastomosis with reconstruction of lacrimal sac, *248
Nyctalopia: See Night Blindness

Obituaries:
Batten, Rayner Derry, 257
Blaauw, Edmond Eduard, 349
Finlay, Charles Edward, 346
Gifford, Sanford Robinson, 340
Hamburger, Carl, 557
Johnson, George Lindsay, 256
Koller, Carl, 344
May, Charles H., 103
Pfingst, Adolph O., 347
Vogt, Alfred, 172

O'Connor Cinch Operation: See Strabismus
Occupational Diseases: See Industrial Diseases
Oguchi's Disease: See Night Blindness
Ointments, ophthalmic, 353
Onchocerciasis, ophthalmoscopic observation of microfilarias in vitreous of patients infected with onchocerciasis, 353
O'Neill, H.: Binocular refraction with cross cylinder technic, 267
Ophthalmia: See also Conjunctivitis: Eyes, diseases; Keratoconjunctivitis
Egyptian: See Trachoma
electric; "arc flash" conjunctivitis; actinic conjunctivitis from electric welding arc, 107
electric; measuring eye flash from arc welding, 260
electric; treatment of photophthalmia following exposure to rays of welding arc, 108
Gonorrheal: See Gonorrhea
sympathetic; prolapse of uvea; treatment and significance in interpretation of sympathetic ophthalmia and glaucoma, *232
Ophthalmologic societies, directory of, 121, 183, 271, 359, 445, 565
Ophthalmology, Brazilian, aspects of, 440
emergency room service at Wills Hospital, *211
history; ocular tuberculosis; its relation to general tuberculosis, *541

Ophthalmology—Continued
research in Royal Canadian Navy, 263
Teaching: See under Education
University of Kansas School of Medicine, 102
Ophthalmoplegia: See Paralysis
Ophthalmoscopy: See Eyes, parasites
Optic Chiasm, problem of split macula; study of visual fields, *43
Optic Disk; Optic Papilla: See Nerves, optic; Neuritis, optic
Optic Tract: See Nerves, optic
Orbit, emphysema; study of 7 cases, 561
improved technic for implantation of ball in Tenon's capsule, 443
orbital metastasis from tumor of pancreas, 113
recurrence of fibrosarcoma 7 years after removal; results of roentgen irradiation, 265
restoration of lower cul-de-sac, 353
socket after enucleation and artificial eye, *18
two plastic operations for repair of orbit following severe trauma and extensive comminuted fracture, *323
Orthoptics: See also Strabismus
appraisal of value of orthoptic clinic in private practice, *503
examinations for technicians, American Orthoptic Council, 339
in aviation, 263
Oxygen, deficiency; cataract produced by anoxia, *259

Palsy: See Paralysis
Pancreas, orbital metastasis from tumor of, 113
Pannus: See Trachoma
Papilledema: See Neuritis, optic
Paralysis, chronic ophthalmoplegia externa, 261
of divergence due to cerebellar tumor, *299
operative treatment of paralysis of external rectus muscle, *254
pupillographic studies; periodic sympathetic spasm and relaxation and role of sympathetic nervous system in pupillary innervation, *74
Parasites: See Eyes, parasites
Paratyphoid, sub-hyaloid hemorrhage following "T. A. B." inoculation, 111
Parents' role in orthoptic training, 442
Parinaud's Disease: See under Conjunctivitis
Pascal, J. I.: Ocular occluders, 170
Pemphigus, virus isolated from pemphigus-like keratoconjunctivitis, 258
Penicillin and gramicidin as ocular chemotherapeutic agents, *165
general and local administration of, 114
in treatment of gonorrheal conjunctivitis: report of case, *162
penetration into eye, *1
Therapy: See Eyes, diseases; etc.
Pentothal Sodium: See Anesthesia
Perera, C. A.: Charles H. May, 103
Periarteritis nodosa, ocular findings in case of, 176
Perimetry: See under Vision
Pfeiffer, R. L.: Location of foreign body in eye with contact lens, 180
*p*H: See Hydrogen Ion Concentration
Pharynx, infection of lymphoid tissue of pharynx and of conjunctiva, *331
Phorias, anomalies of fusion associated with aniseikonia; preliminary report, 265
diagnostic value of monocular occlusion, *316
method of evaluation of binocular muscle balance, 443
near horizontal phoria and duction tests, 353
Photophthalmia: See Ophthalmia, electric
Pigmentation: See also Melanin; Nevi
comparison of ocular reactions of pigmented and albino rabbits to normal horse serum, 559
Pituitary Body, hypertension with tumors of adrenal and pituitary glands, *381
Plastic Surgery, colored moving pictures of plastic surgical procedures on eye, 264
two plastic operations for repair of orbit following severe trauma and extensive comminuted fracture, *323
Pneumococci, production and treatment of experimental pneumococcal hypopyon ulcers in rabbit, 355
Poisons and Poisoning: See under names of substances, as Gas; etc.
Poliosis: See Hair, color of
Pollen, A.: Meningococcic conjunctivitis, *284
Preeclampsia: See Eclampsia
Pregnancy, hypertension associated with preeclampsia and eclampsia of pregnancy, *381
Premature Infants, fibroblastic overgrowth of persistent tunica vasculosa lentis in infants born prematurely, 175
Pressure: See Blood, pressure; Tension
Pringle-Bourneville's Disease: See Sclerosis, tuberous
Prowazek Bodies: See Trachoma
Pseudoaphakia Fibrosa: See Lens, Crystalline
Pseudoisochromatic Plates: See Color Blindness
Pseudoxanthoma elasticum; angioid streaking of retina, 110
Psychoses: See Neuroses and Psychoneuroses
Ptosis: See Eyelids, ptosis
Pupils, choline esterase at nerve termination in sphincter pupillae of turtle, 440
choline esterase in amphibian sphincter pupillae, 350
di-n-butylcarbaminolycholine sulfate: new cycloplegic and mydriatic drug, *289
effect of mydriatics on intraocular pressure in so-called primary wide-angle glaucoma, 177
pupillographic studies; periodic sympathetic spasm and relaxation and role of sympathetic nervous system in pupillary innervation, *74
Tonic: See Reflex, pupillary
Purkinje Image: See Retina, blood supply
Purtscher's Disease: See Retina, blood supply
Pyelonephritis, fundus oculi in urologic diseases associated with systemic hypertension, *427

Ramsey, G. A. S.: Retinal arterial tension associated with epilepsy, 264
Reading, effect of astigmatism on visibility of print, 561
Records: See Case Records
Recruits: See also Military Medicine
causes of impaired vision in recently inducted soldiers, *399
ocular malingering, *223
ophthalmic requirements of military services: changes from Feb. 1, 1943 to Jan. 1, 1944, *160
Red Cross Institute for the Blind (1918-1925), story in relation to present problem of war blinded, 177
Reflex, pupillary; nervous factor in origin of simple glaucoma, *384
pupillary; pupillary reactions of seemingly unaffected eye in clinically unilateral simple glaucoma; pupillographic contributions to diagnosis of glaucoma in preclinical stage, *392
pupillographic studies; periodic sympathetic spasm and relaxation and role of sympathetic nervous system in pupillary innervation, *74
Refraction: See Accommodation and Refraction
Rehabilitation of uniocular patient, 440
story of Red Cross Institute for Blind (1918-1925) in relation to present problem of war blinded, 177
Reprints, Bielschowsky's "lectures on motor anomalies of eyes" available, 270
Retina: See also Macula Lutea
angiomatosis retinae (von Hippel-Lindau disease); report on genealogic tree, 261
Blood Supply: See also Thrombosis; etc.
blood supply; angioid streaking of retina, 110
blood supply; changes in fundus of eye in various forms of arterial hypertension, *376
blood supply; evaluation of ocular angiospasm, *453
blood supply; further observations on autofundoscopy (auto-ophthalmoscopy of Eber; Purkinje figure of Walker), 441
blood supply; traumatic liporrhagia retinalis (Verhoeff); Purtscher's disease, *191
detachment; modification of Arruga's speculum, 109
detachment resulting from traction exerted by intraocular foreign body, 179
diabetic retinopathy, *96
entoptic methods in clinical investigations, 351
fundus oculi in urologic diseases associated with systemic hypertension, *427

Retina—Continued
hemorrhage: iritis, retinal hemorrhage and changes in lens following injection of typhus vaccine; report of case, *336
Inflammation: See Retinitis; Retinochoroiditis
massive bilateral preretinal type of hemorrhage associated with subarachnoidal hemorrhage of brain, 561
pathologic changes in eye associated with subacute bacterial endocarditis; report of 5 cases with autopsy, *198
retinal arterial tension associated with epilepsy, 264
Retinitis, diabetic, 111, 112
Jensen's: See Retinochoroiditis
pigmentosa, detection and significance of melanophore expanding substance in urine and blood with reference to, 111
pigmentosa: night blindness, improvement with vitamin D, including experimental production of retinitis pigmentosa and its treatment in humans with vitamin D, 113
Retinochoroiditis, chorioretinitis associated with positive serologic tests for Toxoplasma in older children and adults, 110
juvenile macular exudative choroiditis: juvenile disciform degeneration of macula (Junius), *144
Retinopathy: See under Retina
Retinoscopy: See Accommodation and Refraction
Riboflavin, ariboflavinosis as probable cause of vernal conjunctivitis, *214
relation of ariboflavinosis and circumcorneal vascularization as observed in Navy, 263
Robinson, J. S.: Appraisal of value of orthoptic clinic in private practice, *503
Roentgen Rays, Therapy: See under names of organs, regions and diseases, as Orbit; etc.
Roper, K. L.: Diagnostic value of monocular occlusion, *316
Ocular occluders, 338
Rychener, R. O.: Appraisal of value of orthoptic clinic in private practice, *503

Sachs-Tay Disease: See under Idiocy
von Sallmann, L.: Penetration of penicillin into eye, *1
Penicillin and sulfadiazine in treatment of experimental intraocular infections with Staphylococcus aureus and Clostridium welchii, *54
Samuels, B.: Pathologic changes in lens associated with nontraumatic iritis, *8
Sarcoidosis, role of sarcoidosis and of brucellosis in uveitis, *469
Sarcoma: See also Cancer; Fibrosarcoma; and under names of organs and regions
primary, of choroid, 354
Scarlett, H.: Juvenile macular exudative choroiditis; juvenile disciform degeneration of macula (Junius), *144
Scars: See under Eyelids
Schaumann's Disease: See Sarcoidosis
Schiøtz Tonometer: See Tension
Schlemm's Canal: See Eyes, physiology
Schlezinger, N. S.: Drusen of optic nerve simulating cerebral tumor, *509
Schoenberg, M. J.: Nervous factor in origin of simple glaucoma, *384
Pupillary reactions of seemingly unaffected eye in clinically unilateral simple glaucoma; pupillographic contributions to diagnosis of glaucoma in preclinical stage, *392
Schools, summary of findings at eye examination of preparatory school boys, 177
visual problems; certain assumptions and data, 113
Sclera, catgut sutures for closure of deep corneoscleral wound in operations for cataract; preliminary report, *321
Surgery: See under Glaucoma
transscleral removal of intraocular foreign body with aid of Berman locator, *207
Sclerosis: See also Arteriosclerosis
multiple, prognosis of, 560
tuberous, 442
tuberous; report of case, *68
Scotoma, use of pseudoisochromatic charts in detecting central scotomas due to lesions in conducting pathways, 351
Scrofula: See Tuberculosis
Sebaceous Glands, tuberous sclerosis; report of case, *68
Section on Ophthalmology, abstracts of articles published in The Journal of American Medical Association under auspices of Section on Ophthalmology, 1943, 434
Sells, S. B.: Experimental studies on fatigue of accommodation; plan of research and observations on recession of near point of accommodation following period of interpolated work on ophthalmic ergograph, *148
Sherman, A. R.: Detachment of retina resulting from traction exerted by intraocular foreign body, 179
Foreign body in lens with formation of cataract; method of extraction, 179
Injury to ciliary body without iridocyclitis, 179
"Shipyard Eye": See Keratoconjunctivitis
Shoemaker, R. E.: Emergency room service at Wills Hospital, *211
Silver Nitrate Therapy: See Foreign Bodies
Sinus, Nasal: See Sinuses, Nasal
Thrombosis: See Thrombosis
Sinuses, Nasal; iridocyclitis and choroiditis due to "silent" sinusitis, 444
Sjögren Syndrome: See Keratoconjunctivitis
Skin, Diseases: See Dermatitis: Herpes; etc.
graft, massive; moving picture demonstration, 563
Skull: See Cranium
Sloane, A. E.: Practical ophthalmic test which furnishes quantitative data; modification of Massachusetts vision test, *217
Smallpox, autoinoculation of eyelids with vaccinia, *539
Snell, A. C., Jr.: Management of corneal lacerations, 180
Societies, Association for Research in Ophthalmology, 102, 339
foreign, directory of, 121, 183, 271, 359, 445, 565
international, directory of, 121, 183, 271, 359, 445, 565
local, directory of, 124, 186, 274, 362, 448, 568
Medical Society of State of New York, Section on Ophthalmology, 339
national, directory of, 122, 184, 272, 360, 446, 566
ophthalmologic, directory of, 121, 183, 271, 359, 445, 565
Pan-American Congress of Ophthalmology, 102, 444
sectional, directory of, 122, 184, 272, 360, 446, 566
state, directory of, 123, 185, 273, 361, 447, 567
Society Transactions:
Canadian Ophthalmologic Society, 262
College of Physicians of Philadelphia, Section on Ophthalmology, 563
New York Academy of Medicine, Section of Ophthalmology, 116, 179, 265, 356
Solandt, D. Y.: Ophthalmologic research in Royal Canadian Navy, 263
Space perception; orthoptics in aviation, 263
Spaeth, E. B.: Massive skin graft; moving picture demonstration, 563
Traumatic liporrhagia retinalis (Verhoeff); Purtscher's disease, *191
Spectacles: See Glasses
Speculum, Arruga's, modification of, 109
Spinal Cord: See Meninges; Nervous System; etc.
Spinal Fluid: See Cerebrospinal Fluid
Squint: See Strabismus
Staphylococci, penicillin and sulfadiazine in treatment of experimental intraocular infections with Staphylococcus aureus and Clostridium welchii, *54
staphylococcic thrombophlebitis of cavernous sinus; report of case, with recovery with chemotherapy and heparin, *329
Stereoscopy: See under Vision
Stocker, F. W.: Alfred Vogt, 172
Strabismus, appraisal of value of orthoptic clinic in private practice, *503
colored moving pictures of plastic surgical procedures on eye, 264
convergent, with high congenital myopia, 443
evaluation of orthoptic instruments, 350
operative treatment of paralysis of external rectus muscle, *254

Strabismus—Continued
operative treatment of squint, 102
parents' role in orthoptic training, 442
relationship of orthoptic treatment to surgery, 561
visual phenomenon related to binocular triplopia, 353
Strandberg-Grönblad Syndrome: See Pseudoxanthoma elasticum; Retina, blood supply
Sugar, H. S.: Binocular refraction with cross cylinder technic, *34, 269; correction, 339
Sulfadiazine: See Cataract; Eyes; etc.
Sulfonamides, Therapy: See Cataract; Conjunctivitis; Eyes, diseases; etc.
Suprarenals: See Adrenals
Surgery: See Apparatus; Instruments; Sutures; and under organs and diseases, as Cornea; Eyelids; Eyes; Glaucoma; etc.
Plastic: See Plastic Surgery
Sutures, catgut sutures for closure of deep corneoscleral wound in operations for cataract; preliminary report, *321
corneoscleral, 262
Swan, K. C.: Di-n-butylcarbaminoylcholine sulfate; new cycloplegic and mydriatic drug, *289
Syphilis: See also under names of organs, regions and diseases
ocular, diagnosis of, 176

Tay-Sachs Disease: See under Idiocy
Tears: See Lacrimal Organs
Tenon's Capsule: See Orbit
Tension: See also Glaucoma
differences of tension in chambers of eye; report of case, 175
modifications of tonometer, *334
Theodore, F. H.: Causes of impaired vision in recently inducted soldiers, *399
Congenital opacities of cornea, *138
Meningococcic conjunctivitis, *245
Thrombosis, bilateral, of posterior calcarine arteries with sparing of macular vision, 352
staphylococcic thrombophlebitis of cavernous sinus; report of case, with recovery with chemotherapy and heparin, *329
Thyroid, monocular exophthalmos due to hyperthyroidism in patient with Duane syndrome, 116
Tissue: See Cells
Tonometer: See Tension
Tonometry: See Tension
Tonsils, infection of lymphoid tissue of pharynx and of conjunctiva, *331
Townes, C. D.: Adolph O. Pfingst, 347
Toxoplasmosis, chorioretinitis associated with positive serologic tests for Toxoplasma in older children and adults, 110
Trachoma, infectivity of, 354
infectivity of; further experiments on antigenicity of virus, 258
Transplantation: See under Cornea; etc.
Trauma: See also under Cataract; Cornea; Eyes; Face; Head; etc.
traumatic liporrhagia retinalis (Verhoeff); Purtscher's disease, *191
Triplopia: See Accommodation and Refraction
Troncoso, M. U.: Development of anterior peripheral synechiae in experimental acute glaucoma, *481
Tuberculosis: See also under special structures of eye and names of diseases
ocular, experimental studies; study of increased resistance to reinoculation after recovery from ocular tuberculosis shown by immune-allergic rabbit, *413
ocular; its relation to general tuberculosis, *541
Tularemia, Parinaud's oculoglandular syndrome, 258
Tumors: See Adenoma; Angioma; Cancer; Fibrosarcoma; Glioblastoma; Melanoma; Neurocytoma; etc.; and under names of organs and regions, as Adrenals; Brain; Cerebellum; Cornea; Eyes; Lacrimal Organs; Orbit; Pancreas; etc.
Tunica Vasculosa Lentis: See Lens, Crystalline
Typhoid, sub-hyaloid hemorrhage following "T.A.B." inoculation, 111
Typhus, iritis, retinal hemorrhage and changes in lens following injection of typhus vaccine; report of case, *336

Ulcers, Corneal: See under Cornea
Undulant Fever, role of sarcoidosis and of brucellosis in uveitis, *469
Urine, detection and significance of melanophore expanding substance in urine and blood with reference to retinitis pigmentosa, 111
Uvea, case of removal of nonmagnetic foreign body from ciliary region, 441
changes in ciliary body after contusio bulbi in which only anterior segment of eye is affected, 107
Inflammation: See also Iridocyclitis; Ophthalmia, sympathetic
inflammation: role of sarcoidosis and of brucellosis in uveitis, *469
inflammation: uveitis associated with Hodgkin's disease; report of case, *517
inflammation: uveitis, dysacousia, alopecia, poliosis and vitiligo; theory as to cause, *520
inflammation: Vogt-Koyanagi syndrome, 444
injury to ciliary body without iridocyclitis, 179
prolapse; treatment and significance in interpretation of sympathetic ophthalmia and glaucoma, *232
Uveitis: See Uvea, inflammation

Vaccinia: See Smallpox, vaccination
Variola: See Smallpox
Vasa Hyaloidea Propria: See Vitreous Humor
Veins, Aqueous: See Aqueous Humor
Retinal: See Retina, blood supply
Viruses: See also Herpes; etc.
infectivity of trachoma; further experiments on antigenicity of virus, 258
isolated from pemphigus-like keratoconjunctivitis, 258
Vision: See also Accommodation and Refraction; Blindness; Eyes, examination; etc.
acuity at low brightness-levels, 562
Color: See Color Blindness; Color Perception
Defective: See also Astigmatism; Myopia; Phorias; etc.
defective; causes of impaired vision in recently inducted soldiers, *399
defective; rehabilitation of uniocular patient, 440
defective; significance of visual defects in war production effort, 435
diagnostic value of monocular occlusion, *316
fusion, projection and stereopsis, 443
ocular malingering, *223
ocular occluders, 170, 338
ophthalmologic research in Royal Canadian Navy, 263
practicability of use of contact lenses at low atmospheric pressures, *326
problem of split macula; study of visual fields, *43
problems; certain assumptions and data, 113
Tests: See also Accommodation and Refraction; Color Perception; Night Blindness; Phorias; Space, perception; etc.
tests; practical ophthalmic test which furnishes quantitative data; modification of Massachusetts vision test, *217
tests; summary of findings at eye examination of preparatory school boys, 177
torsion in persons with no known eye defect, 561
Vitamins: See also Riboflavin
B_2: See Riboflavin
D: night blindness, improvement with vitamin D, including experimental production of retinitis pigmentosa and its treatment in humans with vitamin D, 113
in ophthalmology, 259
Vitiligo: See also Albinism
uveitis, dysacousia, alopecia and poliosis; theory as to cause, *520, 560
Vitreous Humor, ophthalmoscopic observations of microfilarias in vitreous of patients infected with onchocerciasis, 353
sub-hyaloid hemorrhage following "T. A. B." inoculation, 111
Vogt-Koyanagi Syndrome: See Uvea, inflammation

Waldapfel, R.: Infection of lymphoid tissue of pharynx and of conjunctiva, *331
Rhinocanalicular anastomosis, *432

Waldman, J.: Drusen of optic nerve simulating cerebral tumor, *509
War: See also Aviation and Aviators; Military Medicine; Naval Medicine; etc.
significance of visual defects in war production effort, 435
story of Red Cross Institute for Blind (1918-1925) in relation to present problem of war blinded, 177
visual acuity at low brightness-levels, 563
Welding: See Eyes, injuries
Weskamp, C.: Bowen's disease of cornea, *310
Wetting Agents: See Detergents
White, N. G.: Di-n-butylcarbaminoylcholine sulfate; new cycloplegic and mydriatic drug, *289
Wills Hospital, emergency room service at, *211
Wong, W. W.: Penicillin and gramicidin as ocular chemotherapeutic agents, *165
Woods, A. C.: Experimental studies of ocular tuberculosis; study of increased resistance to reinoculation after recovery from ocular tuberculosis shown by immune-allergic rabbit, *413
Role of sarcoidosis and of brucellosis in uveitis, *469
Wright, W. W.: Technic of enucleation of eye, with implantation of prosthesis, 263
Zentmayer, W.: Abstracts of articles published in The Journal of American Medical Association under auspices of Section on Ophthalmology, 1943, 434
Zona: See Herpes zoster